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Vol. 9 OCTOBER, 1936 No. 4

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

Official Organ for
THE AMERICAN ACADEMY OF PEDIATRICS

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Vol. 9, No. 4, October, 1936. Journal of Pediatrics is Published Monthly by The C. V. Mosby Company, 3523 Pine Blvd., St. Louis, Mo. Subscription price: United States, its possessions, Pan-American Countries, $8.50 a year; Canada, $9.00; Foreign, $9.50. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879.

The Journal of Pediatrics

VOL. 9 OCTOBER, 1936 NO. 4

Original Communications

PROTAMINE INSULIN IN CHILDREN

GLADYS L. BOYD, M.D.
TORONTO, ONTARIO

EVER since insulin was first used, attempts have been made to alter it in such a manner that its absorption would be delayed and its action would be made to resemble more closely that of the normal pancreatic secretion. Efforts during the same time to make the insulin pure have helped to defeat this purpose by reducing the zinc content[1] of the compound and possibly by eliminating split protein products, both of which play a rôle in delaying the absorption of the hormone.

A little over two years ago, Hagedorn and his coworkers[2] at the Steno Memorial Hospital in Copenhagen felt justified in subjecting to clinical trial a mixture of insulin and protamine which they had found after prolonged search to be less soluble in serum and more slowly absorbed than any mixture previously suggested. In the course of some other work these observers discovered that insulin combined with nucleic acid had a more acid isoelectric zone than insulin itself. Accordingly, they sought some basic group with which to combine insulin in order to get its isoelectric zone nearer the pH of tissue fluid than insulin hydrochloride. Such a compound would act as an acid, whereas ordinary insulin acts as a base. Various substances were tried, but protamines alone gave solubility results sufficient to merit trial. Monoprotamines only have been used. The raw material has been the ripe sperm of certain fish. In the past two and a half years these authors have treated eighty-five patients with such a mixture. No ill effects have been seen and much better control has been established in severe cases. These workers used ordinary insulin in the morning and the protamine compound at night.

Presented before The American Pediatric Society, Bolton Landing, June, 1936.
From the Wards and Laboratories of the Hospital for Sick Children, Toronto, and the Department of Paediatrics, University of Toronto, under the direction of Prof. Alan Brown.

Early this year, Root, White, Marble and Stotz[3] reported a series of cases with equally good results. A little later, Kerr, Best, Campbell, and Fletcher[4] reported their results in man and animals, and more recently Sprague and his associates[5] have added further confirmation of the possibilities of this insulin.

The present report is based on the study of twenty-five diabetic children treated with protamine insulin since last December at the Hospital for Sick Children, Toronto. At first the insulin used was made with ordinary insulin mixed with protamine obtained from Hagedorn by Best. Later the protamine was obtained from British Columbia salmon and prepared at the Connaught Laboratories, Toronto. The insulin is prepared for injection by adding to ordinary insulin the right quantity of protamine buffered by sodium phosphate. A flocculent precipitate forms which after shaking is injected in the usual manner. This compound is unstable and should be used within ten days of its preparation. When it is kept in the ice box, a certain amount of shrinkage of the protamine solution occurs, so that it must be warmed to room temperature again before measuring. This instability of the compound is one of the difficulties that must be overcome because it entails too much handling of material by unskilled hands.

The usual procedure has been to observe the patient in the hospital with alternating control periods on insulin hydrochloride with those on protamine insulin. A few of those treated have been well-stabilized cases treated in the out-patient clinic, but in all these close observation of both urine and blood sugar was made.

In none of the children studied was control impossible with ordinary insulin, but in some this was accomplished only with four doses of insulin a day, one before each meal and one at midnight. With protamine insulin alone, or combined with ordinary insulin, equally good, if not better, results were achieved with two doses a day. In both Copenhagen and Boston it was usual to use morning doses of ordinary insulin and evening doses of protamine insulin. In a few this has been found an advantage, but in most cases the "insulin retard" has been used entirely because it is less confusing for the parents to give one kind than to give two kinds. The object of combining the two has been to get the advantage of quick acting insulin to cover the postprandial rise of blood sugar after breakfast. In our experience, the morning glycosuria has been equally well controlled if the protamine insulin was administered by the clock, 8 A.M. and 8 P.M., rather than at mealtimes. Kerr found this adjustment more satisfactory in controlling blood sugar curves in dogs, and it was on his suggestion that we tried it. There is what might be called a refractory period before the best results are obtained. Substitution of equal doses of protamine insulin for ordinary insulin, even if given

by the clock, may permit some glycosuria for a couple of days, which completely disappears without any further adjustment by the end of this time. Patients requiring from 80 to 100 units of insulin daily are satisfactorily controlled with two doses of the new insulin or one dose of new and one of old. In milder cases requiring up to as much as 50 to 60 units daily, adequate control is often possible with only one dose in twenty-four hours. The optimum time for its administration is not fixed, but at present an hour before breakfast has seemed a suitable time. It may prove to be better to administer the single dose between eight and nine o'clock at night.

Reactions occur, but they are less severe and less frequent than hypoglycemia. Possibly this is because of the more gradual fall of the blood sugar that occurs. One is amazed how often with a blood sugar content of 40 to 50 mg. per 100 c.c. no symptoms or signs of reaction are apparent, whereas values between 20 and 30 are frequently only accompanied by mild symptoms. Blood sugar estimations appear to be more urgent in the patient who is a glycosuric with insulin retard than with ordinary insulin. Protracted ill feeling, such as tiredness and weakness, due to hypoglycemia is more common and is sometimes sufficiently severe to make the patient desire a return to the old insulin. Such feelings of course may be overcome by the needed reduction of the dose. The well-adjusted patients, on the other hand, speak of increased well-being and particularly about the new restfulness or peacefulness of their sleep. The time of a reaction is, of course, much longer after the insulin is given, usually at least ten hours later, often much longer. Rest is not only more complete for the child, but, as his reactions are more likely to occur in the late afternoon or at breakfast time, the parents rest in greater security. If frequent blood sugar examinations are not made, very severe reactions may develop before symptoms occur. These are not frequent fortunately, but we have seen several patients with blood sugars of 15 to 20 mg. in whom intravenous glucose administration was necessary.

So far, no local reaction has been observed as the result of the administration of protamine insulin, nor has any general protein reaction occurred. There has been no more rapid improvement in carbohydrate tolerance than in those equally well controlled with ordinary insulin. In fact, as Hagedorn himself pointed out, there is no advantage offered by the new insulin to those easily controlled by ordinary insulin, unless this necessitates too frequent needle punctures.

Protamine insulin acts so slowly that it is contraindicated when quick action is desirable, such as in coma, when better results are obtained with ordinary insulin. Likewise in preoperative cases it should not be given, even if the patient is taking it and is being well controlled by it under ordinary circumstances.

SUMMARY

The discovery of protamine insulin is a distinct advance in diabetic therapy. It offers as good or better control of the disease with fewer doses in the day.

Reactions are fewer and, at least for the child, usually occur at more convenient periods when the child is at home, and not during his sleep.

There is a wider margin of safety in errors either in the dose of insulin given or in the food taken.

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A COMPARISON OF THE ANTIRACHITIC EFFECT OF IRRADIATED CHOLESTEROL AND COD LIVER OIL

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and Alan Brown, M.D.
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In 1934, Waddell[1] irradiated cholesterol and found that the resultant product had a marked antirachitic effect on rats and chickens. He reported that this product differed from irradiated ergosterol in that it was equally as effective in the cure of rickets in chickens as was cod liver oil, rat unit for rat unit. During the past five winter months we have investigated the antirachitic value in humans of irradiated cholesterol in comparison with that of cod liver oil.

The procedure used was similar to that employed by us in previous investigations on the antirachitic effect of various substances.[2, 3, 4] The observations were made on normal healthy infants varying in age from one to six months at the initial examination (Table I). The infants were practically all of British and Northern European stock.

Table I

Ages of Infants in Months at Time of Initial Examination

Group	Under 1 mo. of age	1 mo. of age	2 mo. of age	3 mo. of age	4 mo. of age	5 mo. of age	6 mo. of age	Total
Irradiated cholesterol	0	15	12	21	17	10	2	77
Cod liver oil	0	13	21	13	17	6	4	74
No vitamin D	1	12	19	18	16	7	2	75

They were attending the infant welfare centers throughout the city and represented a cross-section of the infant population of Toronto. We are indebted to Dr. Gordon P. Jackson, Medical Officer of Health of the City of Toronto, for his cooperation and assistance. Every infant was observed over a period of five winter months. The initial examination was made in October or November, 1935. A second examination was carried out in January, 1936, while the final examination was made in the month of March or April. Each time a physical examination was made and x-ray films were made of both wrists. The infants were all artificially fed on either fresh cow's milk or evaporated milk dilutions. Care was taken to see that none of this milk contained any added vitamin D. Vitamin D free cereals were usually added to the diets at about five months of age. Vegetables

From the Department of Paediatrics, University of Toronto, and the Hospital for Sick Children, Toronto.

were included in the diet at six to eight months of age. Practically none of the infants received egg yolk during the period of observation. Almost all the infants gained in weight either at or above the expected rate.

The infants were divided into two groups. To one group was administered 150 international vitamin D units daily in the form of cod liver oil. This oil was a mixed specimen of cod liver oils obtained from a number of pharmaceutical houses and was of such potency that the daily dose of 20 drops contained exactly 150 international vitamin D units. (One tablespoonful of average good cod liver oil contains 330 international vitamin D units.) The other group received 150 international vitamin D units daily in the form of 10 drops of a solution of irradiated cholesterol in corn oil.* We were also able to observe a third group of infants who received no vitamin D throughout the period of observation.

In order to check thoroughly on the home conditions and to insure that instructions were being carried out, an exceedingly capable public health nurse visited each home every two to four weeks during the period of observation. Occasionally it was found that the instructions were not being accurately observed, and in these instances the infants were discarded from the observation. As previously reported,[2, 3, 4] we found that the usually accepted clinical signs, namely, craniotabes and moderate epiphyseal or costochondral enlargement, were not reliable in the diagnosis of rickets.

We are indebted to Dr. Martha Eliot, Assistant Chief, Children's Bureau, Department of Labor, Washington, D. C., who very kindly interpreted the x-ray findings. The reading of the plates was done without any knowledge as to the antirachitic therapy employed. The degree of rickets was classified by Dr. Eliot as 1–, 1, 2, and 3. In this paper we have called Dr. Eliot's Group 1–, extremely slight rickets (a barely perceptible change which frequently might not be noted); Group 1, mild rickets (a slight but obvious rachitic change); and Groups 2 and 3, moderate and marked rickets (well-defined fringing and cupping at the end of the bone). In addition, the x-ray films were interpreted by Dr. Eliot as to the presence or absence of active advancement of the rachitic process. It should be noted that this last classification indicates only the state of activity of the rachitic process and does not indicate in any way the degree of rickets.

In Table II is given the degree of rickets which was found in the infants of the different groups at the initial examination. It would

*We are indebted to Abbott Laboratories, Parke, Davis & Company, and Squibb & Sons for the cod liver oil used in this investigation.
We are indebted to E. I. Du Pont de Nemours & Company for the irradiated cholesterol. The cholesterol (containing the provitamin) was irradiated and after irradiation the unchanged cholesterol was separated from the small fraction which had been activated. This active fraction (containing the vitamin D) was dissolved in corn oil.
Six independent assays were made by different laboratories, including ourselves, in order to check on the vitamin D potency of the products.

seem that the distribution of the cases showing evidences of extremely slight or mild rickets is fairly equally divided among the three groups with the exception that there were slightly more cases with mild rickets in the group receiving irradiated cholesterol.

TABLE II

DEGREE OF RICKETS AT THE INITIAL EXAMINATION IN AUTUMN

GROUP	TOTAL CASES	NO RICKETS (PER CENT)	EXTREMELY SLIGHT RICKETS (PER CENT)	MILD RICKETS (PER CENT)	MODERATE AND MARKED RICKETS (PER CENT)
Irradiated cholesterol	77	84	10	6	0
Cod liver oil	74	91	8	1	0
No vitamin D	75	88	11	1	0

In Table III is shown the maximum degree of rickets observed at any time subsequent to the initial examination.

TABLE III

MAXIMUM DEGREE OF RICKETS OBSERVED AT ANY TIME SUBSEQUENT TO INITIAL EXAMINATION

GROUP	TOTAL CASES	NO RICKETS (PER CENT)	EXTREMELY SLIGHT RICKETS (PER CENT)	MILD RICKETS (PER CENT)	MODERATE AND MARKED RICKETS (PER CENT)
Irradiated cholesterol	77	82	8	10	0
Cod liver oil	74	69	19	12	0
No vitamin D	75	51	16	20	13

In Table IV is given the number of cases in each group showing actively advancing rickets with no evidence of healing at times of observation. As stated before, this classification indicates only the presence of activity in the rachitic process and does not indicate in any way the degree of rickets.

TABLE IV

NUMBER OF CASES SHOWING ACTIVELY ADVANCING RICKETS WITH NO EVIDENCE OF HEALING AT THE TIMES OF OBSERVATION

	TOTAL CASES	AUTUMN (PER CENT)	MIDDLE OF WINTER (PER CENT)	END OF WINTER (PER CENT)
Irradiated cholesterol	77	9	1	1
Cod liver oil	74	7	5	3
No vitamin D	75	9	21	31

In a previous communication[5] we reported that the administration of vitamin D in the form of irradiated cholesterol produced rapid healing of acute rickets during the winter months. Since this report we have observed six additional infants, varying in age from five to ten months, all exhibiting x-ray evidence of moderate or marked rickets. During the winter months we administered to each of these infants 750 inter-

Fig. 1. Fig. 2.

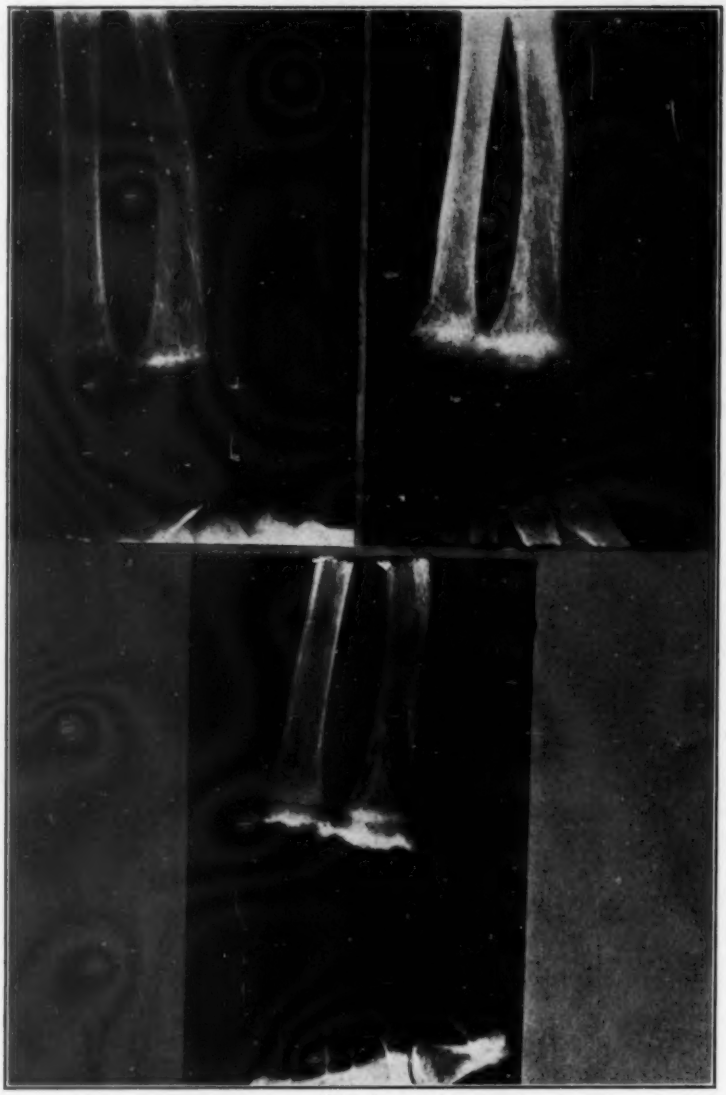

Fig. 3.

Fig. 1.—Case No. 173. X-ray film of wrist of infant aged ten and one-quarter months, showing evidence of marked rickets, April 9, 1935.

Fig. 2.—Case No. 173. X-ray film of wrist of same child after the daily administration for two weeks of 750 international vitamin D units of irradiated cholesterol.

Fig. 3.—Case No. 173. X-ray film of wrist of same child after the daily administration for one month of 750 international vitamin D units of irradiated cholesterol.

national vitamin D units daily in the form of irradiated cholesterol. In every instance marked healing resulted. X-ray pictures taken two weeks and one month after administration was started showed evidences of the healing (Figs. 1, 2, and 3). Also we observed during March and April, 1936, the effect of the daily administration of 300 international vitamin D units of irradiated cholesterol to each of three infants who exhibited moderate or marked rickets. Their ages varied from six to eight months. The weather in Toronto during these two months was so inclement that there was no possibility of the infants receiving any antirachitic effect from exposure to sunshine or skyshine. (The Dominion Meteorological Department reports that in Toronto the month of April, 1936, was the darkest April on record.) Again, in all three cases marked healing resulted (Figs. 4 and 5).

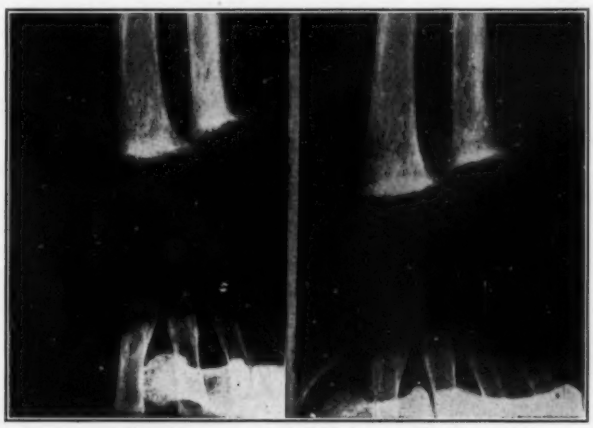

Fig. 4. Fig. 5.

Fig. 4.—Case 102. X-ray film of wrist of infant aged seven and one-half months, showing evidence of marked rickets, March 17, 1936.

Fig. 5.—Case 102. X-ray film of wrist of same child after receiving 300 international vitamin D units of irradiated cholesterol daily for one month.

DISCUSSION

The results reported in Table III show that no infants receiving 150 international vitamin D units of either irradiated cholesterol or cod liver oil daily developed moderate or marked rickets, while 13 per cent of the infants receiving no vitamin D developed rickets of this degree. This is a degree of rickets which is of definite concern to the clinician. The number of infants developing extremely slight rickets and mild rickets is somewhat lower in the group receiving irradiated cholesterol than in the group receiving cod liver oil.

In Table IV we see that 31 per cent of the infants receiving no vitamin D exhibited active rickets at the concluding observation in March

or April, while only 3 per cent of the group receiving cod liver oil and 1 per cent of the group receiving irradiated cholesterol showed any evidences of actively advancing rickets.

It is evident from Figs. 1 to 5 that the daily administration of 750 or 300 international vitamin D units in the form of irradiated cholesterol not only prevented the development of rickets but brought about rapid healing of severe rachitic processes.

CONCLUSIONS

1. The antirachitic value of 150 international vitamin D units administered daily to infants in the form of irradiated cholesterol is equally or possibly slightly more effective than 150 international vitamin D units in the form of cod liver oil.

2. The daily administration for five winter months of 150 international vitamin D units in the form of irradiated cholesterol or cod liver oil to 151 normal infants of British or Northern European stock prevented the development in every instance of rickets of a moderate or marked degree.

3. Seven hundred fifty or 300 international vitamin D units administered daily in the form of irradiated cholesterol effectively healed moderate and marked degrees of rickets in infants of British or Northern European stock.

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ANEMIA OF THE NEWBORN

Report of a Case With Especial Reference to Etiology and Therapy

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Ecklin[1] in 1919 was the first to report in detail a case of anemia of the newborn. In 1932 Arthur Abt[2] reviewed fifteen cases reported up to that time, and in 1935 Abbott and Abbott[3] added twenty-six new cases bringing the total number up to forty-one; with the subtraction of seven doubtful cases, this leaves a total of thirty-four unquestioned cases. Since then, a number of other cases have appeared in the literature (Schwartz,[4] Dennett and Ashton,[5] Cohen,[6] Brown, Morrison, and Meyer,[7] Pasachoff and Wilson,[8] Hotz,[9] Dedichen,[10] Noll,[11] and Mannheimer.[12]

The symptoms and signs have been frequently reviewed and need not be reiterated here. Abbott and Abbott[3] report twenty-two cases with a color index of one and above, and six cases below one. The etiology is obscure, so much so that it has been called idiopathic anemia of the newborn. Diamond, Blackfan, and Baty,[13] have shown that erythroblastosis fetalis is associated with universal edema of the fetus, icterus gravis neonatorum, and anemia of the newborn. While erythroblastosis is not present in all cases, there can be no question that there is some relationship between anemia of the newborn and universal edema and icterus gravis. Ecklin[1] and Diamond, Blackfan, and Baty[13] have reported the familial incidence of icterus gravis and anemia of the newborn, and recently Pasachoff and Wilson[14] have done the same for universal edema and anemia of the newborn. Though Pasachoff and Wilson[8] report a mortality of 12 per cent, the prognosis as a rule is good. Some recover without treatment, in others blood transfusions and iron and liver extract have been used either alone or in various combinations.

Baby T. W. was brought to me on Jan. 8, 1936, at the age of twenty-seven days with the following history: He was born on Dec. 12, 1935, in a small Wisconsin town at full term after normal labor and delivery without instrumentation. The birth weight was 7 pounds 5 ounces (3,300 gm.). The father and mother were in good health, and a two-year-old brother was living and well. The mother had vomited at irregular intervals throughout pregnancy, but her blood pressure and urine had remained normal; except for some loss of weight, she felt well. Since the mother was unable to furnish breast milk, the infant was placed at various times on plain milk dilutions, evaporated milk mixture, and S. M. A. Shortly after birth the father (a physician) noticed gradually increasing pallor, but placed no great stress on this.

Read before the American Pediatric Society, June 13, 1936.

At no time was jaundice noted. At the age of three weeks the infant began to vomit regularly (a frequently reported symptom of this disease) and lose weight, and when change of food brought no relief, he was brought to me for examination. Physical examination revealed a well-developed, markedly undernourished infant (weight 3,540 gm.) with marked dehydration as evidenced by poor tissue turgor and depressed fontanel. The pallor of the skin and mucous membranes was very noticeable. The spleen and liver were not palpable, and the examination was otherwise negative. The infant was admitted to Abbott Hospital where a blood examination revealed a hemoglobin content of 42 per cent (Sahli), a red blood count of 1,380,000, and a color index of 1.5. Because of the evident concentration of the blood, the absolute values were undoubtedly still lower. Three hundred cubic centimeters of normal saline solution was injected subcutaneously, and the following morning an intravenous transfusion of 100 c.c. of the father's blood was given.

TABLE I

DATE	HG. (SAHLI)	R.B.C.	W.B.C.	PMNS.	LYMPH.	MONO.	EOS.	BASO.	NORMOBLASTS	PLASMA CELLS	TÜRCK'S IRRITATION CELLS
1/ 8/36	42	1,380,000	30,500	46.0	41.5	8.5	2.0	1.0	9.0	0.5	0.5
1/ 9/36	57	2,870,000	14,950	77.1	19.0	2.6	1.3		9.0		
1/10/36	57	2,720,000	17,750	52.0	40.0	5.0	2.0		1.0	1.0	
1/13/36	58	2,120,000	15,650	40.0	49.0	4.0	6.0		1.0	1.0	
1/14/36	53	2,240,000	14,600	22.0	69.0	5.0	3.0	1.0	5.0		
1/16/36	48	2,040,000									
1/18/36	45	1,840,000									
1/21/36	52	2,510,000	13,800								
1/23/36	58	2,990,000									
1/25/36	56	2,510,000									
1/28/36	58	3,050,000	9,000	25.0	67.0	5.0	2.0	1.0			
1/30/36	60	2,660,000									
2/ 1/36	60	3,050,000									
2/12/36	52	2,550,000	7,500	30.0	56.0	10.0	3.0			1.0	
2/22/36	63	3,190,000	9,700	22.0	62.0	4.0	8.0			3.0	1.0
3/ 6/36	65	3,020,000	7,500	40.0	55.0	2.0	3.0				
3/20/36	75	3,800,000	11,850	40.0	56.0	2.0	2.0				
4/11/36	65	3,340,000	11,550	50.0	47.0	2.0	1.0				
4/24/36	71	3,630,000	13,500	34.0	64.0	1.0	1.0				
5/15/36	80	4,060,000	10,750	42.0	55.0		3.0				
7/ 1/36	82	4,250,000	12,900	52.0	48.0						

1/8/36 Blood Groups (Moss)
Baby Group 2
Father Group 2
Mother Group 2

1/9/36 Fragility Test
Hemolysis begins at 0.46% and is complete at 0.38%
Control (4-day-old baby from nursery)
Hemolysis begins at 0.44% and is complete at 0.32%

Wassermann (Kolmer and Kline)
Baby Negative 1/17/36
Father Negative 5/15/36
Mother Negative 5/15/36

1/9/36 Urine
Color—straw
clear
Reaction—acid
Sp. Gr.—1.012
Albumin—very faint trace
Sugar—negative
Pus cells—0-1
Bacteria—few

1/14/36
Platelet count—340,000
Reticulated R.B.C.—4.4%

1/23/36
Reticulated R.B.C.—11.8%

4/25/36
Hemoglobin
Mother—74

2/22/36
straw
cloudy
acid
1.032
negative
faint trace
0-1

5/15/36
Gastric fluid
Free HCl—0
Comb. Ac—54
pH—4.4

There was a rapid rise in hemoglobin and erythrocytes which, however, quickly spent itself (Chart 1). On January 18, ten days after admission, the hemoglobin and red blood cells had sunk close to their levels on admission. On that date, 1 c.c. of liver extract* was injected intramuscularly and repeated at forty-eight-hour intervals for three doses. The effect on the blood was so immediate and so spectacular and the improvement in the infant's general well-being was so marked, that it was very difficult to ascribe it to anything else than the specific effect of the liver. The reticulocytes were 4.4 per cent on January 14, and on January 23 they had risen to 11.8 per cent. After three further injections, the baby was discharged from the hospital. During the twenty-six days of his stay, his feeding consisted of from 720 to 1,000 c.c. of two-thirds lactic acid milk with 5 per cent dextrimaltose No. 1, which produced a gain of weight from 3,540 gm. to 4,520 gm. Viosterol, ten drops, and orange juice were given daily. The infant's temperature was normal throughout

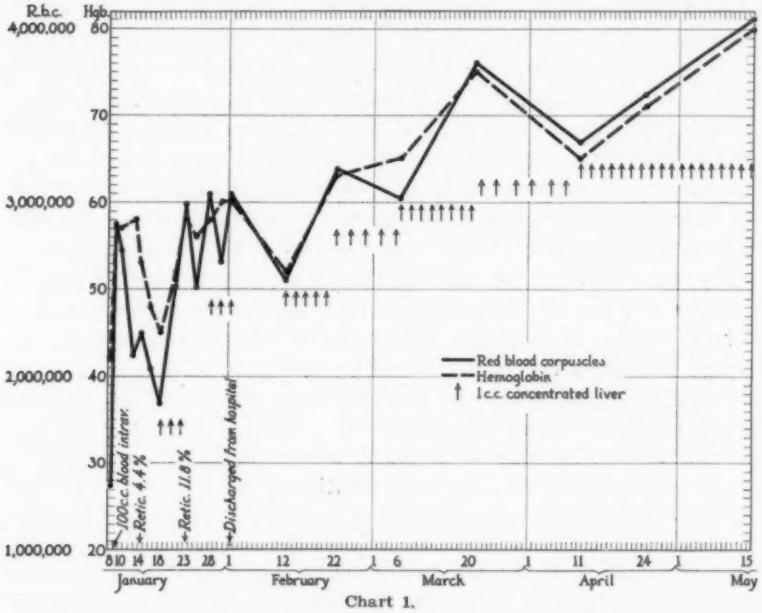

Chart 1.

except for slight temporary elevations due to the blood transfusion and liver injections. The blood Wassermann tests of the infant and both parents were negative. The patient was brought back on February 12 for examination and showed a marked drop in hemoglobin and red blood cells, though it had gained in weight (5,010 gm.). It had received no liver during that time. It was returned home and given 1 c.c. liver intramuscularly every second day. On the next visit, February 21, the blood values had again risen. From February 22 to March 6 liver was given every third day, with a slight drop in red blood cells, though not of hemoglobin. From March 6 to 20 the injections were increased to every two days with a definite increase in the red blood cells and the hemoglobin, to be followed by a decline when the liver was given but twice a week from March 20 to April 11. Thereafter it was given every other day up to May 15, when treatment was discontinued. During the entire time

*Concentrated solution of liver extract (Lederle) 1 c.c. contains active material obtained from 100 gm. liver.

from February 1 to May 15, the infant's diet consisted of equal parts of evaporated milk and water with 5 per cent dextrimaltose, viosterol or oleum percomorphum, ten drops a day, and gradually increasing amounts of orange juice. He received no other food and no medication.

Liver and liver extract have been reported a number of times in the treatment of anemia of the newborn. M'Neil,[15] Gelston and Sappinger,[16] Abbott and Abbott,[3] Dedichen,[10] Hotz,[9] Henry,[17] and Mannheimer[12] have used liver treatment, but in conjunction with iron and multiple blood transfusions, so that it is difficult to judge the specific effect of the liver. When Schwartz[4] gave his patient lextron (containing liver extract, yeast and iron) ½ capsule twice a day, the blood picture remained stationary, but when he increased the dose to one capsule three times a day, the hemoglobin and erythrocyte count immediately improved; his patient recovered without any other treatment. Admittedly, anemia of the newborn is a disease which tends toward spontaneous recovery, and while this fact makes difficult the evaluation of any therapy, our results in this case and those of Schwartz point very definitely toward the specific effect of liver in this condition. If confirmed in future cases, considerable light will be thrown on the hitherto unknown etiology.

The use of liver in anemia is due to the experimental work of Whipple and the clinical observations of Minot and Murphy in pernicious anemia. Castle[18] has shown that the antianemic principle in liver is formed by the interaction of an extrinsic factor derived from beefsteak, yeast, etc., with an intrinsic factor formed by the mucosa of the stomach. The liver stores the substance elaborated by the stomach after it has been acted upon by the extrinsic factor. While Greenspon[19] has attacked the interpretation of the rôle played by the extrinsic factor, there has been no successful challenge of Castle's fundamental work, that pernicious anemia is caused by the permanent absence of the intrinsic factor. There are several diseases besides pernicious anemia, in which the formation or storage of the antianemic principle is interfered with. The one of special interest to us is the so-called pernicious anemia of pregnancy, or, better, macrocytic anemia of pregnancy. In this condition which occurs in the later months of pregnancy, there is a temporary diminution or absence of the antianemic principle; the symptoms are relieved by liver extract and do not recur after the pregnancy has terminated, even though liver is discontinued (Strauss[20]). In anemia of the newborn, we seem to have the same temporary absence of the antianemic principle. The possibility of some relation between macrocytic anemia of pregnancy and anemia of the newborn is suggested by the work of Wintrobe and Shumacker,[21] "Comparison of Hematopoiesis to Macrocytic Anemia of Pregnancy and Anemia in Infants": "It is our im-

pression derived from the study of the changes which take place in the size and number of the red blood corpuscles of the fetus, as well as in the proportion of erythroblasts and reticulocytes, that in many respects the blood of the developing fetus resembles that of cases of pernicious anemia which are being subjected to an effective, continuous and extremely potent stimulus to blood formation. It would also appear from our studies that the macrocytosis of the newborn, frequently considered to be the result of physicochemical changes in the blood, really represents a final stage in the development of the blood in the fetus. In comparison with the blood in pernicious anemia, the blood of the newborn is similar to that of cases in incomplete remission." They then suggest that antianemic principle of Castle may be the same substance which causes development of the blood of the fetus and that when a pregnant woman fails to secrete a sufficiency of this substance for both herself and the fetus, one or two things may happen: either the infant receives more than its share, causing macrocytic anemia of pregnancy, or the mother retains the major portion of the antianemic principle, causing anemia of the newborn. They further state that liver therapy has not had a satisfactory trial in primary anemia of the newborn, nor in erythroblastosis of the newborn, the blood picture and findings of which suggest pernicious anemia. This is an interesting working hypothesis and is partially confirmed by our apparent success with liver treatment in anemia of the newborn. Future cases of this disease should be subjected not only to clinical tests of liver therapy, but also to specific tests for the presence of the intrinsic factor. Singer[22] has reported that neutralized normal gastric juice injected into rats produced a definite reticulocyte response, which was absent when the gastric juice of pernicious anemia patients was used, indicating the absence of the intrinsic principle. By the employment of this method or other similar tests, the etiology could be definitely established.

SUMMARY

A case of anemia of the newborn is reported in which improvement followed immediately injection of liver extract. Large doses of liver seem to be necessary. The success of this treatment, if confirmed in future observation, should be of definite aid in clearing up the hitherto unknown etiology of this disease.

I am indebted to Miss Elneita Foscue for technical assistance with the blood examinations.

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HEMATOLOGY AND PATHOLOGY OF APLASTIC ANEMIA OCCURRING IN A FIVE-YEAR-OLD CHILD

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IN 1888 Ehrlich,[14] describing a case of a young woman twenty-one years old who developed an extremely severe anemia following incessant uterine bleeding, proposed the name of "aplastic anemia" because of a total absence of regenerative reaction on the part of the bone marrow. From several reviews of the literature made by Cabot,[13] Hirschfeld,[22] Musser,[35] Frank,[16] Smith[41] and Herrman,[20] it may be assumed that over one hundred cases of aplastic anemia are on record, although roughly in about one-third of this number autopsy studies are lacking. It is true that aplastic anemia produces so characteristic a blood picture that no errors in diagnosis are possible; yet such a diagnosis must always be confirmed by the histologic study of the marrow and of other hemopoietic tissues. It must further be emphasized that a typical aplastic blood picture may frequently develop secondary to various other pathologic processes, particularly in acute leucemia and sepsis. For this reason it is preferable, as Bigler and Brennemann[10] have done in reporting their series of cases of "sepsis with granulocytopenia," to avoid the use of the term "aplastic anemia" in describing secondary or symptomatic aplasia.

The occurrence of true aplastic anemia in infancy and childhood must still be regarded as quite a rare occurrence, the greatest majority of reported cases having been encountered in adults. The first pediatric case was probably recorded by Silva[43] (1894) who, however, termed the condition "progressive pernicious anemia." This report was followed by one by Muir[34] (1900), by Acuña[2] (1904), by Babonneix and Paisseau[6] (1910) and by de Elizalde[15] (1913). The first definitely authentic case of aplastic anemia in a child to be recorded in the American literature was that of Smith[41] (1919). The earlier case of Larrabee[27] (1911) reported under the name of "aplastic anemia" showed a lymphatic hyperplasia with evidence of myeloblastic activity. This raises the question whether the condition might not have been one of acute leucemia without leucocytosis. Including both the authentic and probable cases, a total of about thirty instances of aplastic anemia in children are now found in the pediatric literature and are summarized in Table I. The largest series have been published by Morquio and Volpe[33] (1933) from the Children's Clinic of Montevideo. Of the eight cases reported by these authors, the first two had been previously published by Lasnier[28, 29]

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(1921 and 1922), and the last is a case of aplastic reaction occurring in the course of acute leucemia.

TABLE I

SUMMARY OF CASES OF APLASTIC ANEMIA IN CHILDREN*

AUTHOR (YEAR)	NO. OF CASES	SEX	AGE (YR.)	DURATION	HB (%)	R.B.C. (MILL.)	W.B.C.	MARROW
Silva (1894)	1	M	12	15 wk.	–	–	–	–
Muir (1900)	1	M	14	2 mo.	12	0.60	7,000	Fatty
Acuña (1904)	1	F	9	1 mo.	–	1.50	4,200	–
Babonneix and Paisseau (1910)	1	F	11	–	25	2.00	–	Fatty
de Elizalde (1913)	1	M	13	–	–	–	–	–
Babonneix and Tixier (1913)	1	F	5	3 mo.	15	0.38	2,000	–
	2	M	11	12 mo.	15	0.55	1,200	Fatty
Heubner (1915)	1	M	2	6 mo.	10	0.98	7,800	Fatty
Kleinschmidt (1915)	1	F	8	6 mo.	10	1.00	3,000	Aplastic
	2	F	4.5	2 yr.	22	0.82	5,800	Fatty
Acuña (1915) Case 2	1	M	3.5	2 mo.	25	1.20	4,500	Fatty
Gorter (1916) Case 1	1	M	6	–	17	0.70	1,600	Yellow
Benecke (1917) Case 1	1	M	3.5	–	18	0.64	2,000	–
Smith (1919)		M	6	8 mo.	10	0.40	4,000	Fatty
Thursfield (1921)	1	F	11.5	7 mo.	30	1.14	5,200	Fatty
Lasnier (1921)	1	F	3	2 mo.	30	1.51	3,500	?
Lasnier (1922)	1	F	11	8 days	–	0.75	–	Fatty
Agnew (1924)	1	F	12	5 mo.	22	1.20	3,500	Fatty
Hurt (1928) Case 1	1	M	13	–	17	0.82	1,800	Fatty
Orrico (1929) Case 2	1	M	2.5	1 mo.	26	1.44	4,600	Fatty
Milhit et al. (1932)	1	F	5	–	8	1.80	6,080	–
Macera et al. (1933)	1	F	10	5 yr.?	20	0.50	6,000	–
Lindquist (1933)	1	M	4.5	acute	25	1.64	200	–
Morquio and Volpe (1933)								
Case 3	1	M	7	3.0 mo.	10	0.75	2,600	Aplastic
Case 4	2	M	8	1.5 mo.	30	1.00	2,500	Fatty
Case 5	3	M	3	3.0 wk.	52	2.50	5,000	Aplastic
Case 6	4	M	3.5	2.0 mo.	15	1.30	1,000	–
Case 7	5	F	9	1.0 mo.	20	1.00	4,500	Aplastic
Greenwald (1934)	1	F	2	6.0 mo.	10	0.75	2,200	Fatty
Osato et al. (1934) Case 5	1	F	11	7.0 mo.	30	1.14	5,200	Fatty

*A number of cases reported under the name of aplastic anemia in children are purposely excluded from the above list on the grounds that either the clinical or hematological features are atypical, or pathological studies are lacking or contradictory. These omissions refer to the following cases: Benecke (Case 4), Gibson, Gorter (Case 2), Herrman, Hurt (Case 2), Kharina-Marinucci, Larrabee, Morquio and Volpe (Case 8), Orrico (Case 1), Parkinson, and Spak. References to Silva and de Elizalde were not available.

It is clear from the above summary that aplastic anemia in infants and children is still sufficiently rare to warrant an additional report. The present case, of which a fairly adequate hematologic study has been

made, followed by a complete histologic examination of all important organs at autopsy, is presented as an addition to the list of authentic cases of aplastic anemia.

CASE REPORT

The patient, a white female child of five and one-half years, was brought to the hospital in a critical condition on Nov. 20, 1935, with a history of recurrent, exsanguinating epistaxis of two months' duration. Bleeding was so severe and persistent as to necessitate cauterization and nasal pack and even then the hemorrhage was controlled only with difficulty. In all, four such hemorrhages had occurred during the two months, and three weeks prior to hospital admission two blood transfusions had been given. The history disclosed the fact that the child was very fond of the odor of gasoline and kerosene and often would saturate her handkerchief with them.

Physical examination upon admission revealed a waxy, pale exsanguinated child, apparently in a comatose condition. Respirations were deep and labored. The nostrils were filled with clotted blood. The lips were pale, and the tongue dry and plastered with dark blood. The tonsils and cervical lymph nodes were not enlarged. Large bubbling râles were heard over both lungs, but no dullness was noted. The heart was greatly enlarged, the left border being in the anterior axillary line and a systolic murmur of functional type, heard at the apex, was transmitted along the sternum and to the axilla. The rate was 160 per minute, the pulse imperceptible. No masses were palpated in the abdomen, and liver, spleen and kidneys could not be felt. No purpuric spots were seen anywhere on the skin. Two incisions, one on the inner aspect of each thigh, about 10 c.m. long (from previous blood transfusions), were noted, and the one on the right was gangrenous for about 2 c.m. at its lower end.

TABLE II

HEMATOLOGICAL CHART OF PATIENT DURING HOSPITALIZATION

(A TOTAL OF 18 TRANSFUSIONS WAS GIVEN DURING THE PERIOD STUDIED)

DATE	R.B.C.	W.B.C.	Hb. (G.M. %)	PLATELETS	L (%)	N (%)	E (%)	B (%)	M (%)	Pl. (%)	Ret. (%)
10/21/35	1.44	2,100	3.6	13,000	75	16	1	0	4	4	0.1
10/22/35	1.52	1,900	3.6	30,000	77	14	0	0	7	2	0.7
10/23/35	2.11	2,050	5.6	40,000	65	24	0	0	8	3	–
10/24/35	2.59	3,500	7.5	75,000	72	12	0	0	10	6	0.3
10/25/35	2.38	2,050	7.7	42,500	78	6	0	0	5	11	0.2
10/26/35	3.50	3,300	9.1	48,000	76	12	0	0	4	8	0.8
10/28/35	3.50	2,600	8.8	20,000	85	4	0	0	8	9	0.2
10/29/35	2.78	2,450	8.4	27,000	89	2	0	0	4	5	0.1
10/31/35	2.71	2,100	6.5	32,500	83	5	0	0	4	5	0.2
11/ 1/35	2.20	1,400	6.0	22,500	85	4	0	0	7	5	–
11/ 2/35	2.39	1,500	6.5	27,500	90	3	0	0	4	3	0.2
11/ 4/35	3.06	1,750	7.0	42,500	81	4	0	0	6	9	0.3
11/ 6/35	3.67	1,600	9.5	32,500	84	6	0	0	2	8	0.1
11/ 8/35	3.83	1,050	9.3	42,500	91	4	0	0	0	5	0
11/10/35	2.97	800	8.8	12,200	85	3	0	0	6	6	0
11/11/35	1.91	660	5.0	63,000	94	1	0	0	2	3	0

Abbreviations: R.B.C., erythrocytes in millions; W.B.C., leucocytes; Hb., hemoglobin concentration in grams per cent (Newcomer); L., lymphocytes; N., neutrophiles; E., eosinophiles; B., basophiles; M., monocytes; Pl., plasma cells; Ret., reticulocytes.

Examination of the blood (tabulated in Table II) disclosed the true nature of the disease. The urine contained a few red cells and hyaline casts and occasional white blood cells; the specific gravity varied from 1.020 to 1.023. The stool gave a negative test to benzidine. Blood cultures were reported to have yielded *B. coli* on one occasion and *Streptococcus viridans* and *B. coli* on another. The first roentgenologic examination (Oct. 23, 1935) revealed a pronounced enlargement of the heart which, however, was found to be slightly decreased in size on the second examination (Nov. 9, 1935). In the last named examination, a mottling about the trunks in the right and upper left lung fields was interpreted to signify the presence of patchy bronchopneumonia. There was also a slight increase in peribronchial markings. (Figs. 1 and 2.) The long bones showed no changes on both examinations (Fig. 2 and 3).

The patient's condition gradually progressed toward fatal termination twenty-six days after admission, the entire course being characterized by a steady, high fever (up to 41° C. at one time) which just before death rose to a height of 42° C. A total of eighteen transfusions were given as listed in Table III.

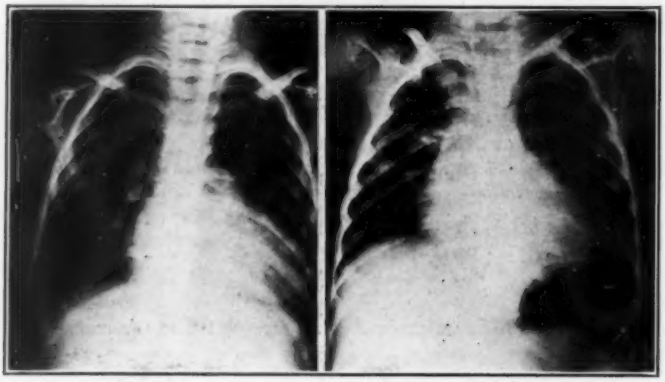

Fig. 1. Fig. 2.

Fig. 1.—Roentgenogram of chest (Oct. 23, 1935) showing an enlargement of cardiac shadow.

Fig. 2.—Roentgenogram of chest (Nov. 9, 1935) showing a decrease in cardiac shadow.

The treatment consisted of iron medication together with cod liver oil and yeast tablets in proper doses. On one occasion a preparation of liver extract was given by injection, but the reticulocyte response, though noticeable, was only transient. Administration of yellow bone marrow extract in large doses had no appreciable effect on the blood picture.

TABLE III

DATE	AMOUNT (C.C.)	DATE	AMOUNT (C.C.)
10/19/35	275	10/30/35	150
10/20/35	200	10/31/35	200
10/21/35	125	11/ 1/35	150
10/22/35	150	11/ 2/35	150
10/23/35	130	11/ 3/35	150
10/24/35	150	11/ 4/35	175
10/25/35	150	11/ 5/35	225
10/27/35	250	11/ 6/35	165
10/30/35	215	11/11/35	200

POSTMORTEM EXAMINATION

The essentials of the anatomic diagnosis at autopsy performed two hours after death were: Marked generalized anemia—aplastic anemia type. Hypoplasia and fatty replacement of bone marrow. Hemorrhages into the skin, pleura, lymph nodes,

Fig. 3. Fig. 4.

Figs. 3 and 4.—Roentgenograms of the left arm and leg (Nov. 9, 1935).

subserosa of the uterus and cecum, and of the mucosa of the esophagus, stomach, duodenum, rectum, ureters, and urinary bladder. Atrophy of the thymus. Hyperplasia of the spleen and the tracheobronchial lymph nodes. Marked erythrophagia in the liver, spleen, and lymph nodes. Right lobar pulmonary gangrene; disseminated lobular pulmonary gangrene in each lower lobe. Gangrenous necrosis of the gums and rectal mucosa. Acute ulcerations of the jejunum and lower ileum. Hemosiderin

staining and fatty degeneration of the liver. Hypertrophy, anemia, and cloudy swelling of the myocardium. Cloudy swelling of the kidneys. Hydropericardium. Focal fibrinous pleuritis. Healing surgical incision over the right upper thigh. Patent foramen ovale.

External Appearance.—The body was that of an emaciated, slender, white, female child, 44.5 inches in length and weighing 32 pounds. The skin was pale, dry and subicteric while the sclerae were icteric. At various places the skin of the trunk and extremities showed petechial and purpuric hemorrhages and an occasional fading ecchymosis. The oral mucous membranes were very pale. The teeth were loosened by marked gangrenous necrosis of the gums. The teeth, buccal mucous membranes, and gums were covered by blackish material, resembling blood, which had apparently oozed from the gums. Over the upper end of each great saphenous vein was a recent surgical incision. That on the left was healed while the one on the right showed some blackish, gangrenous necrosis. The superficial lymph nodes were not enlarged, and there was no edema.

Body Cavities.—The pleural cavities contained no excess fluid, and there were no pleural adhesions. Under the pariental pleura bilaterally were many hemorrhages measuring up to 0.5 cm. in size. The pericardial cavity contained an excess of clear yellow fluid, estimated at 50 c.c. in volume. The heart, the right chambers of which were flabby and overdistended, was greatly enlarged. Its transverse diameter in situ was increased, the apex extending past the midclavicular line. The subcutaneous, subperitoneal and mesenteric fat was pale and small in amount. The mesenteric and retroperitoneal lymph nodes were consequently very conspicuous although not increased in size. A peculiar, irregular blotchy red color also helped render them easily visible. The diaphragm was in normal position. The liver edge was just below the costal margin. There was no excess peritoneal fluid.

Mouth and Pharynx.—As a consequence of the severe necrosis of the gums previously described, the teeth were loosened, and, rigor mortis having set in, the pharynx could not be examined without danger of pushing out the teeth.

Thyroid and Thymus.—The thyroid was not palpably enlarged. Only indefinite traces of thymic tissue remained in the fat at the site of the thymus.

Heart and Blood Vessels.—The enlarged heart, empty but with 1 cm. of aorta, weighed 140 gm. (normal is 90 gm.). The external configuration was slightly altered because of the overdistention of the right chambers. The pericardium was smooth; the epicardial fat, pale and scanty in amount. The myocardium was of an extremely pale, grayish pink color and in it were small focal areas of yellowish fatty change. The wall of the right ventricle measured 2 to 3 mm. while the left ventricular myocarium was 4 mm. thick at the apex and 10 mm. at the base. The chambers contained small, pale postmortem blood clots and pale, watery fluid blood. There were no defects in the valves and no changes in the coronary arteries. The foramen ovale had a defect 4 mm. in diameter which could not be covered by a fold of endocardium. A few small, yellow intimal thickenings were present in the first part of the aorta. The remainder of the aorta, the pulmonary arteries, and the inferior vena cava exhibited no change.

Lungs.—The mucosa of the main bronchi was covered by a tenaceous, slimy exudate, and it was pale. The very pale left lung weighed 110 gm. (normal is 112 gm.). The upper lobe, except for petechial pleural hemorrhages, was normal. The pleura of the lower lobe also had petechial hemorrhages. Throughout this lobe were numerous irregular areas of peribronchial consolidation varying from a few millimeters to several centimeters in diameter. These areas were dark reddish black in color and were extremely conspicuous because of the pronounced paleness and bloodlessness of the surrounding uninvolved portions of the lung.

The right lung was more voluminous and heavier than the left, weighing 200 gm. (normal is 115 gm.). The posterior half of the upper lobe was the site of a

sharply demarcated, uniform dark reddish black consolidation. The overlying pleura was roughened by fibrin. The surface made by cutting this peculiar type of consolidation was dry, dark, and not especially friable. The anterior half of this lobe was relatively normal and pale. The middle lobe, except for petechial pleural hemorrhages and hyperemia in its posterior part, was not abnormal. The right lower lobe resembled the left lower lobe.

Liver and Gallbladder.—The liver was enlarged, weighing 865 gm. (normal is 620 gm.). The organ was pale; the capsule, thin and smooth; and the margin, rounded. The surfaces made by cutting bulged markedly. On them the lobular markings were almost indistinguishable on the pale pinkish brown background. There was very little fat and no apparent increase in connective tissue. The gallbladder and the extrahepatic bile ducts were not abnormal.

Spleen.—The spleen was enlarged and weighed 70 gm. (normal is 52 gm.). It was deep purplish red in color, firm, and had a smooth tense capsule. The cut surface of the pulp was moderately firm and the malpighian bodies just discernible.

Pancreas.—There was no recognizable gross abnormality.

Gastrointestinal Tract.—The esophageal mucosa had a few petechial hemorrhages. In the gastric mucosa petechial hemorrhages were very numerous, becoming confluent in a few places. The gastric contents were not blood stained. The duodenal mucosa gave evidence of hyperemia and a few petechial hemorrhages. The tips of the plicae in the lower portion of the duodenum were hyperemic and in a few places were acutely ulcerated in areas measuring several millimeters in diameter. Similar acute ulcerations measuring up to 15 mm. in diameter were present in the mucosa of the ileum. They were not related to Peyer's patches and were most numerous in the terminal part of the ileum. At the base of the appendix and around the tip of the cecum was a subserous hemorrhage. The cecal and rectal mucosa showed a diffuse hyperemia and a few petechiae. The anus was the site of a group of gangrenous ulcers, the largest of which measured 3 mm. They had foul, necrotic bases and reddish black margins.

Adrenals.—The adrenals appeared normal for the age.

Kidneys.—The kidneys were markedly enlarged, together weighing 205 gm. (normal is 131 gm.). The right kidney was very pale and had a yellowish cast on the cut surface. This surface bulged out markedly. The capsule stripped with ease leaving a smooth surface. The cortex was widened, measuring 6 to 7 mm. in thickness. The cortical markings were indistinct. The renal pelvis showed little alteration. The left kidney in all essential respects resembled the right.

Urinary Tract.—An occasional petechial mucosal hemorrhage was present in the urinary bladder and in the ureter.

Generative Organs.—Subserous petechial hemorrhages covered the fundus of the uterus. The ovaries, fallopian tubes, and vagina were normal for the age. There were no ulcers in the latter.

Lymph Nodes.—The superficial lymph nodes were not enlarged. The tracheobronchial nodes were enlarged and on the cut surface showed a dark reddish brown, moist discoloration. The abdominal nodes were not enlarged but were very conspicuous because of the wasting and paleness of the subperitoneal fat and also because of their color. They were irregularly mottled a red or brown color, although parts of some nodes and all of others were normally grayish pink.

Muscular System.—The muscles were very pale and revealed considerable wasting.

Skeleton and Bone Marrow.—The vertebral bone marrow of the midthoracic region was pinkish red in color and that of the lower lumbar region a very pale pinkish gray. The rib marrow was normally red. The extreme upper end of the right femur contained fatty, yellow marrow. In the lower end of the upper third the marrow became pinkish gray mottled with red. This mottling of both the femur and vertebral marrows was not due to foci of hematopoiesis but to hemorrhage as the microscopic examination subsequently revealed.

Brain and Spinal Cord.—No examination was made.

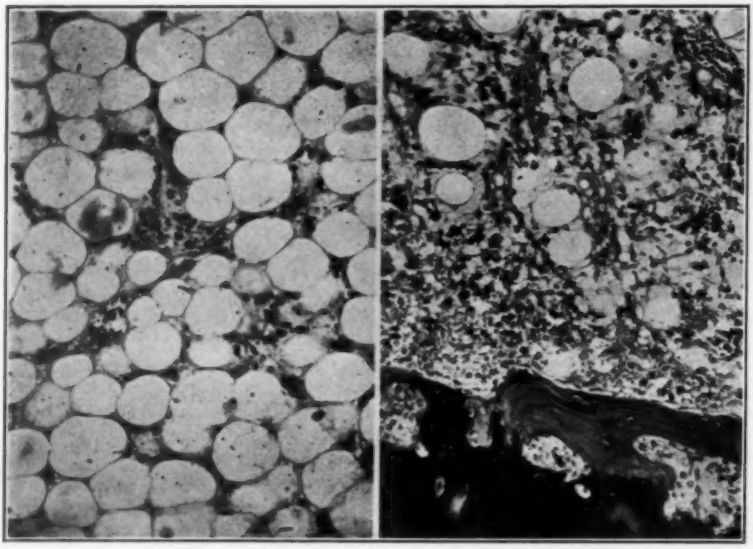

Fig. 5. Fig. 6.

Fig. 5.—Photomicrograph of a section of femur marrow showing a hemopoietic focus surrounded by extensive fatty tissue. This focus is the most cellular one of all the foci seen in the section. Hematoxylin eosin, ×285.

Fig. 6.—Photomicrograph of a section of rib marrow showing the most active portion of the myeloid tissue, adjacent to the cartilage. Hematoxylin eosin, ×285.

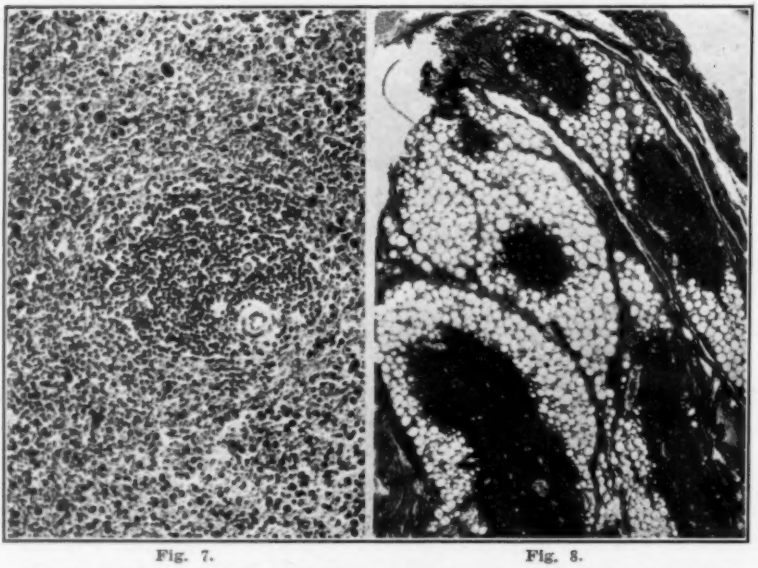

Fig. 7. Fig. 8.

Fig. 7.—Photomicrograph of a section of the spleen showing an atrophic condition of malpighian bodies and an increase of reticulum cells. Hematoxylin eosin, ×285.

Fig. 8.—Photomicrograph of a section of the thymus showing a marked atrophy of thymic parenchyma, due to fatty infiltration, the thymic tissue being represented by a few reticulum cells in the connective tissue stroma. Hematoxylin eosin, ×65.

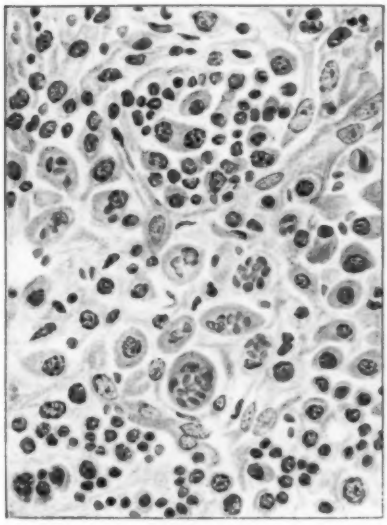

Fig. 9.

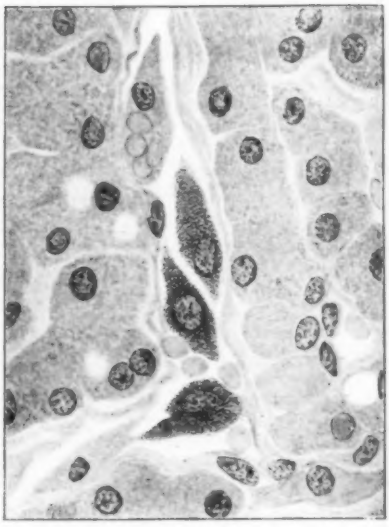

Fig. 10.

Fig. 9.—Camera lucida drawing from a section of the lymph node showing a small follicle surrounded by an accumulation of large reticulum cells with ingested intact erythrocytes. Hematoxylin eosin azur, 4 mm. objective, 10 ocular.

Fig. 10.—Camera lucida drawing from a section of the liver showing several Kupffer cells containing intact erythrocytes and iron pigment in a hepatic sinusoid. Prussian blue stain, counterstained with hematoxylin, oil immersion lens, 10 ocular.

HISTOLOGIC STUDY

The histopathologic study is based on the study of tissues fixed in Zenker's formol and formalin, embedded in celloidin and stained with hematoxylin and eosin, hematoxylin eosin-azur, Scharlach R and by the Prussian blue method for iron

Bone Marrow.—Femur marrow, both pale and red, rib marrow, and upper dorsal and lumbar vertebral marrow were examined. The marrow was found to be fatty with a slight amount of gelatinous edema (Fig. 5). The predominating cells were lipophages, hemophages and plasma cells. Small karyorrhexic lymphocytes and occasional regenerating megakaryocytes were seen between the fat cells. No evidence whatever of erythropoiesis or of granulopoiesis was encountered. One eosinophilic myelocyte was found. In all sections the red color observed grossly was found to have resulted from hemorrhage into the marrow and not from foci of hemopoiesis. Prussian blue stains revealed much iron in the macrophages in addition to the intact red cells shown by other stains. The rib marrow answered to the above description also, but in addition it contained more plasma cells, some of which resembled Maximow's polyblasts (Fig. 6). The vertebral marrow was essentially the same as that of the ribs and femur, but with the addition of an occasional small lymphoid cell nodule and possibly an occasional degenerating myeloblast.

Spleen.—The malpighian bodies were small and were characterized by a reticulum cell increase throughout (Fig. 7). Many of these cells were in mitosis. Lymphorrhexis was pronounced. The outstanding splenic change, however, was a reticulum cell hyperplasia of the pulp and sinuses so extreme as to obscure the latter. Many of these cells were extremely large and actively phagocytic, containing red blood corpuscles and much brown pigment shown by the Prussian blue reaction to be iron.

Thymus.—There was an extreme degree of atrophy, considering the age. Lymphocytes were almost entirely absent, and only a few reticulum cells remained in the connective tissue stroma. Hassall's corpuscles were necrotic (Fig. 8).

Lymph Nodes.—Lymph nodes from three abdominal areas and the tracheobronchial region were examined. They appeared to be normal in size but showed a great decrease in lymphoid tissue. The follicles, small, lymphorrhexic and devoid of reaction centers, were invaded to their centers by large reticulum cells, many of which contained brown pigment resembling iron, while others had ingested one or more intact erythrocytes (Fig. 9). Some of the reticulum cells had several nuclei. The mottled reddish color of the lymph nodes seen at autopsy was found to be caused by a generous invasion of red blood cells in the sinuses. The brown pigment was identified by the Prussian blue reaction as being iron.

Liver.—The liver cells were more or less isolated from one another. In the centers of the lobules they revealed a coarse fatty change and some iron staining (Fig. 11). Here and there were foci of liver cell autolysis apparently due to the great colonies of large bacilli which they contained. The liver sinusoids were unusually wide. The Kupffer cells in them were large and rounded and appeared to be increased in numbers. Many of these cells contained large amounts of iron pigment, while others had engulfed one or more well-preserved erythrocytes (Fig. 10).

Lungs.—The peculiar type of consolidation seen grossly was found to be gangrenous pneumonia. The alveoli in these areas were filled by an exudate which had undergone gangrenous necrosis so advanced that its original cellular nature, except for scattered masses of red blood cells, could not be determined. The alveolar walls were undergoing necrosis, although in a few places stainable nuclei were still evident. Massive bacterial growths of large bacilli had overgrown these areas. The more normal portions of the lungs gave evidence of a slight passive hyperemia and a focal fibrinous exudate. Even in the earliest and most minimal exudates these same large bacilli had caused slight gangrene (Fig. 12).

Kidneys.—The only abnormality noted was a moderate degeneration of the epithelium of the convoluted tubules.

Heart.—The connective tissue showed a mucinous change.

The *adrenal, ovary, pancreas,* and *diaphragm* sections showed no abnormality.

COMMENT

The case here observed presents a typical hematologic and pathologic picture of aplastic anemia. Anemia of this type occurs more frequently in adults than in children for the simple reason that the hemopoietic power of the older individual is more readily exhausted than that of the young. The most distinctive feature of this disease is its unique

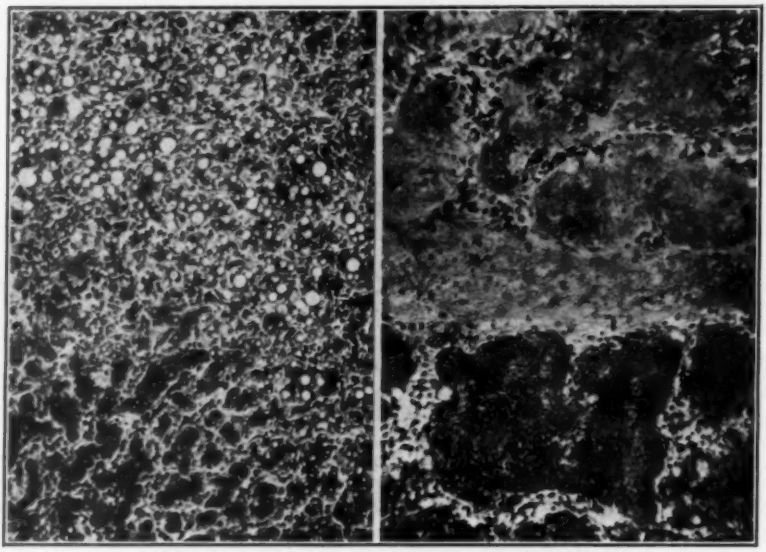

Fig. 11. Fig. 12.

Fig. 11.—Photomicrograph of a section of the liver, showing a central fat necrosis of hepatic lobule, together with an increase in Kupffer cells. Hematoxylin eosin, ×285.

Fig. 12.—Photomicrograph of a section of the lung showing an extensive hemorrhage into the alveoli (lower portion) and an unchecked bacterial growth (upper portion). Hematoxylin eosin, ×300.

blood picture. The decided reduction in the total number of erythrocytes, accompanied by a corresponding diminution in the hemoglobin content, reaches a level seldom seen in any other type of anemia. The lowest figure in children recorded in the literature, namely, 390,000, was observed in a six-year-old female child by Osato and his coworkers, although Ehrlich's original case showed 210,000 in a woman aged twenty-one years. In spite of this great reduction in number, the erythrocytes consistently exhibit no evidence of regeneration. Hypochromia is frequently seen, explaining in part the very low hemoglobin

reading; but anisocytosis, poikilocytosis, and polychromatophilia are practically never encountered. Because the regenerative power of the hemopoietic tissue is abolished, nucleated erythrocytes are never present, and reticulocytes are very scarce. The reticulocyte response, if present at all, to liver therapy or to any other type of medication, is usually transient.

Persistent leucopenia is also characteristic of this disease. It, too, may be extreme, the lowest figure (200 per cm.) having been reported by Lindquist[30] in a case of acute aplastic anemia in a four-and-a-half-year-old male child. In the case here reported the lowest level (600) was reached on the day before death. Agranulocytosis is the only other condition in which such a great reduction in the total number of leucocytes is seen; and, as in agranulocytosis, this diminution occurs primarily in the cells of the myeloid series, there being a great decrease in neutrophilic granulocytes. Eosinophiles and basophiles disappear altogether. Unlike agranulocytosis, however, the neutrophilic granulocytes in aplastic anemia never completely disappear, there being an average of approximately 10 per cent present throughout the course of the disease. This relative neutropenia gives rise to a picture of relative lymphocytosis which, however, is not to be confused with absolute lymphocytosis, for the actual number of the lymphocytes is definitely decreased. As a rule, plasma cells are present up to about 10 per cent of the total white cell count. Another constant feature, and one which may constitute the basis for a hemorrhagic tendency, is a conspicuous reduction in platelet count. On stained smears the platelets are to be found only with great difficulty and the direct chamber count shows a low figure ranging between 10,000 and 75,000. Immature forms of leucocytes are never seen in smears made from the peripheral blood, although indirect and amitotic division of leucocytes may be occasionally demonstrated. Even though the bleeding time is usually prolonged and the coagulation time likewise delayed, the fragility of the erythrocyte against hypotonic salt solution reveals no significant deviation from the normal. No evidence of increased hemolysis or of bilirubinemia occurs in aplastic anemia, the plasma generally being water-clear or slightly pale yellow. Serum bilirubin, upon actual estimation, gives a subnormal value. The urobilin reaction in the urine is negative although a urobilinogen test may be positive.

The final and conclusive diagnosis of aplastic anemia is based upon the histologic findings of the hemopoietic tissues. In the present case not only the myeloid tissue, but practically all the lymphoid elements as well, exhibited a pronounced atrophy. Sections of bone marrow taken from the midfemur and from the end of the rib revealed typical changes. The myeloid elements were replaced by excessive amounts of fatty tissue, with consequent reduction in the cellular components. The sinusoidal

and capillary spaces were filled with a scant amount of blood-forming tissue consisting mostly of lymphoid elements and a few plasma cells. The most remarkable feature of the bone marrow was the decided diminution in the number of megakaryocytes, only a few of which were seen, these being mostly immature forms (megakaryoblasts).

The lymphoid tissue throughout the body was also found to be atrophic in this case. The thymus was reduced to a thin sheet of atrophic reticular elements. The spleen showed striking reduction in the size of the malpighian bodies and the lymph nodes in general exhibited pronounced atrophy of primary follicles. Macrophages were increased in the lymph sinuses and in the splenic pulp, many of which contained intact erythrocytes in their cytoplasm. Hemosiderosis of these organs, as well as that of the liver cells in the portal triangles, explained to some degree the reduction in circulating erythrocytes. The decided erythrophagia of the macrophages may have resulted from the phagocytosis of foreign erythrocytes introduced into the blood stream by repeated blood transfusions. This phenomenon does not necessarily indicate any incompatibility of the transfused blood, but it does signify that the histiocytic system had been stimulated to acute functional activity by repeated blood transfusions.

In the liver a rather constant finding of central fatty changes of hepatic lobules with hemosiderosis of portal areas was very striking. The free iron granules in the Kupffer cells and in a few hepatic parenchyma cells were definitely demonstrated by Prussian blue reaction, indicating some degree of hemolytic process. This demonstration of free iron in the liver and spleen, however, does not necessarily imply classification of aplastic anemia in the general category of hemolytic anemia, inasmuch as hemosiderosis may occur in conditions other than anemia. The remarkable prolific growths of bacterial masses in various portions of the lungs, together with extensive hemorrhages into the alveoli, are also rather frequently observed in aplastic anemia. This picture closely simulates that found in the lungs of patients dying of agranulocytic angina, as previously reported in a five-year-old female child (Kato and Vorwald[24]).

PATHOGENESIS

Aplastic anemia may develop at any age period, but the occurrence of this condition in children is of extreme interest, for the young individuals are provided with rather reactive hemopoietic tissues, so that such an anemia as seen in this age period is usually of a normoblastic or hyperplastic type. This at once leads us to a consideration of the pathogenesis of aplastic anemia. Originally Ehrlich considered that a severe and chronic hemorrhage may lead to the aplasia of myeloid tissue, but this assumption was controverted by the experiments of Blumenthal and Morawitz,[12] who produced a typical anemia of aplastic type by re-

peated hemorrhage; but the hematology of their experimental animals differed from that of clinical aplastic anemia in that the marrow showed an increase in lymphocytes. The closest approximation in experimental production of aplastic anemia was achieved by Selling,[39, 40] with chronic intoxication of animals with benzol. His clinical observation of chronic benzol poisoning in industrial medicine corroborated his experimental results. In the case here reported, the history revealed the patient's fondness for the odor of gasoline and kerosene, although it is quite doubtful that such transient inhalation of volatile gas could instigate a fatal anemia of this type. It is to be admitted that the myeloid tissue of this patient may have been so labile as to lead to a state of profound aplasia, following an insignificant degree of intoxication.

As far as our case is concerned, the pathogenesis must be sought in the assumption of a general blood poison acting upon the labile hemopoietic tissue, producing the fatal anemia accompanied by leucopenia and thrombocytopenia. This assumption conforms to the idea of Hirschfeld, who considered aplastic anemia to be undoubtedly erythrotoxic in nature and not a simple aregeneration. Pappenheim regarded aplastic anemia as a form of pernicious anemia, not due to primary myelopathy, but secondary to erythromyelotoxicosis. Both these authors, therefore, use the terms "aregeneratory" or "hyporegenerative" anemia. Frank, on the other hand, characterized the disease as a form of essential thrombopenia (with "aleukia hemorrhagica" and "panmyelophthisis" as synonyms). Our case may with propriety be designated as that of essential erythroleucothrombopenia. Additional synonyms suggested by others are: amyelia (Klemperer); anmyelhemia (Kaznelson); toxic paralytic and anhemopoietic anemia (Schneider); anémie par anhémopoiese (Aubertin); myélose globale aplastique (Morquio and Volpe); and anemia aplastica gravis (Macera and his associates). "Aplastic hemolytic anemia" (Türck) is apparently a misnomer, as there is very little evidence that hemolysis plays any significant part in the causation of the disease. Likewise, the classification of aplastic anemia among the so-called erythronoclastic anemias by Parsons and his associates is erroneous.

SYMPTOMS AND COURSE

Aplastic anemia is a subacute fatal disease with a somewhat insidious onset. In a few instances the patient may show noticeable pallor of the skin for a considerable time before any manifestation of definite symptoms. Most usually, however, the sudden hemorrhage, often very severe and uncontrollable, is the first indication of the disease. Following this initial hemorrhage the disease runs a rather rapid course, usually from a few weeks to a few months at the most. True aplastic anemia is incurable, so far as is known. Cases of recovery following repeated blood transfusions (Herrman) are probably not true cases of aplastic anemia.

The disease is usually accompanied by a moderately high fever and increasing weakness. The patient's resistance is greatly undermined because of the profound leucopenia leading to bacterial invasion of vital organs, particularly of the lungs where resulting abscesses or bronchopneumonia usually cause death. Repeated hemorrhages from the mucous membrane are but one factor of the vicious cycle in the production of anemia.

DIAGNOSIS AND TREATMENT

When the typical blood picture is present, the diagnosis of aplastic anemia is comparatively easy. In cases of a doubtful or ambiguous picture, bone marrow biopsy should be resorted to. This condition can without difficulty be differentiated from thrombocytopenic purpura on the basis of the leucocyte count and the final outcome. In aplastic anemia, leucopenia and thrombocytopenia are the rule; while in hemorrhagic purpura, leucocytosis is most usually present. Aplastic anemia is invariably fatal, whereas Werlhof's purpura is not necessarily so. Another condition liable to be confused with aplastic anemia is acute leucemia during the so-called aleucemic stage; the differentiation here consists mainly in the presence of stem cells in leucemia, while in aplastic anemia immature forms practically never appear. The third condition which may give rise to diagnostic confusion is agranulocytosis, in which leucocytes are greatly reduced, with a total disappearance of granulocytes. In aplastic anemia, however, the neutrophilic granulocytes are always present, even though eosinophiles and basophiles may disappear completely. The greatest difficulty in differentiation seems to arise in distinguishing between aplastic anemia and pernicious anemia, for Ehrlich originally used the term "aplastic pernicious anemia" and Pappenheim and others regarded aplastic anemia not as a primary disease in itself but as a form of pernicious anemia. These two conditions, nevertheless, are totally different clinically as well as hematologically. In pernicious anemia the most significant feature is the occurrence of remissions with or without liver therapy, while in aplastic anemia remissions are never encountered and the disease is progressively fatal. The blood picture in pernicious anemia is macrocytic hyperchromic, characterized by poikilocytosis, anisocytosis, polychromatophilia, and showers of normoblastosis, especially during remissions. In aplastic anemia these morphologic characteristics are totally absent. Aplastic anemia is the extreme type of hypoplastic anemia, while pernicious anemia belongs to the category of hyperplastic anemia, a point which in the latter condition predisposes toward a favorable prognosis.

Treatment of aplastic anemia is unsatisfactory. Iron, arsenic, liver extract, bone marrow extract, high vitamin diet, and light therapy are, in practically all cases, ineffective. Blood transfusions give temporary relief but are never curative. Roentgen ray irradiation, advocated in

the treatment of agranulocytosis by Friedmann and Thoma, has also been employed by Osato and his associates[37] in some cases of aplastic anemia. This method, if combined with blood transfusions, is said by them to be the specific curative treatment for aplastic anemia. In fact Osato goes so far as to claim that aplastic anemia is no longer an incurable disease with this combination of treatments. His observations, however, are limited to but two cases of aplastic anemia so treated.

SUMMARY AND CONCLUSIONS

1. A case of idiopathic aplastic anemia occurring in a five-year-old female child, with typical hematology and pathology, is reported.

2. No definite etiologic factor is discernible in this case, although the history of the patient's fondness for the odor of kerosene and gasoline must be noted as playing a possible rôle in causation of the disease in this instance, since these volatile substances may be hemotoxic as is benzol which is regarded as a preeminent leucotoxin.

3. Of the pathologic study the most outstanding finding is the generalized atrophy and aplasia of the hemopoietic organs both of myeloid and lymphoid types.

4. Another interesting finding is the notable erythrophagia of the large phagocytic cells found in the sinuses of the lymph glands and the spleen. The erythrocytes ingested by these macrophages are in all probability the foreign red blood cells introduced into the circulation by blood transfusions, the phagocytic activity of these histiocytes being stimulated by the repeated transfusions. Hemosiderosis in the reticuloendothelial cells as well as in the hepatic parenchyma cells is notable.

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INFLUENZAL MENINGITIS

A Study of Its Clinical Characteristics Based on an Analysis of 54 Cases From the Records of the St. Louis Children's Hospital

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ALTHOUGH the literature contains many admirable articles on the subject of influenzal meningitis, in most instances the authors' interest was primarily bacteriologic, and there has been but little discussion of the clinical features of this disease. During a study of certain aspects of influenzal meningitis, the results of which are recorded elsewhere,[1, 2, 3] a review was made of the fifty-four case records available at the St. Louis Children's Hospital, and it seemed that the clinical features of this group of cases were of sufficient interest to warrant discussion, although the composite picture was one of diversity rather than uniformity. This paper is based largely upon an analysis of these cases, but occasional references have been made to a series of 500 cases collected by one of us (D. W. W.) from reports in the literature. The latter series was compiled with great care, all doubtful cases being excluded. About fifty more cases could have been added, but it was convenient to keep the number at 500.

The structure of this paper may be outlined as follows:

1. Figures on relative frequency of various kinds of meningitis at this hospital, and on incidence by sex and age, on mortality, etc.
2. Clinical aspects of the disease. Predisposing causes, type of onset, duration of illness, etc.
3. Laboratory findings (blood counts, blood cultures, other cultures), spinal fluid, cytology, and bacteriological study.
4. Problems which may arise in differential diagnosis.

Relative Frequency.—In the experience recorded by Neal,[4] *H. influenzae* ranked forth as a cause of purulent meningitis. The experience at this hospital is similar, as shown by the accompanying table which gives the figures for 1918-35.

Meningococcus meningitis	160 cases
Streptococcus meningitis	74 cases
Pneumococcus meningitis	62 cases
Influenza bacillus meningitis	54 cases
Staphylococcus meningitis	22 cases

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Sex and Age.—Only 16 of our 54 patients were females. However, in Neal's group of 111 patients, 59 were females, and it seems likely that our experience in this respect is merely a freak of random sampling. Only 12 of our patients were over two years of age, and here our experience is in accord with the general impression. Of the 500 cases collected from the literature, 127 were in patients more than two years old. The oldest patient in the St. Louis Children's Hospital series was thirteen years old (the hospital admits patients up to the age of fifteen years), and the youngest was two months old.

Mortality.—In our group of fifty-four cases there were three recoveries. Two of these were in patients over two years of age. In the larger series there were thirty-five recoveries, twenty-six of which occurred in patients over two years of age. Clearly the prognosis is not as hopeless in this age period as in infancy.

CLINICAL FEATURES

Onset.—According to the prevailing concept, influenzal meningitis is usually "primary." However, in ten of our cases it seemed clear that the onset of meningitis was preceded by otitis or pneumonia, and in some additional instances there were other features of interest in the recent history. One patient, an eighteen-month-old colored boy, developed osteomyelitis of the tibia following an injury to the ankle and was in the hospital for several days before signs of meningitis appeared. A history of trauma to the skull was obtained in two cases. One of these patients developed meningitis while in the hospital with a fractured skull, while the other, admitted with meningitis, had undergone prolonged manipulation of the middle ear as his physician attempted to remove a foreign body. In the remaining forty cases the meningitis might perhaps be considered "primary," although many of the patients had concomitant otitis and pneumonia. In twenty-five of the forty cases the history was that of an abrupt onset; in the others the onset was more insidious.

Duration of Illness.—In the fifty-one fatal cases the average time elapsing from first symptoms of severe illness to exitus was approximately fourteen days. In the group of cases in which the meningitis was preceded by otitis or pneumonia, the time between the demonstration of meningitis and death averaged slightly less than three days. In the whole series there were two patients who died within two days of the onset of the disease. One of these patients, a white female child sixteen months old, seemed perfectly well the night before admission to the hospital. At 6 A.M. on the day of admission she seemed listless and feverish, at 11 A.M. she vomited, and at 5 P.M. she had a convulsion and was brought to the hospital. On admission she seemed almost moribund, with a temperature of 40.4° C., irregular respiration, and continuous

convulsive movements. Lumbar puncture showed 4,500 cells and many influenza bacilli. Death occurred a few hours after admission. This case indicates that influenzal meningitis can kill with great rapidity, but usually the course is more prolonged. The longest duration in any of our fatal cases was thirty-four days, and in this instance serum treatment may have prolonged the course. However, another patient, who received no serum, lived for twenty-two days after the onset of cerebral symptoms, and the average duration in Rivers' series was twenty days.

Miscellaneous Aspects.—In purulent intracranial infection in young children the conventional meningeal signs are often absent, and influenzal meningitis is no exception to this rule. Reference has already been made to the insidious onset which characterized some of these cases. One must be quick to suspect meningitis in any unexplained febrile illness of an infant. A number of our patients looked remarkably well during a considerable portion of their course.

Extrameningeal Lesions.—Concomitant otitis and pneumonia have already been mentioned. One patient with otitis media had a submaxillary abscess. Two patients developed pleural effusions, and in two others necropsy revealed pericarditis. Metastatic lesions were noted during life in six additional patients. One of these, the child with osteomyelitis of the tibia, has already been discussed. Three other children had abscesses of the extremities, and two had cellulitis. An extensive purpuric eruption was observed on one patient.

LABORATORY FINDINGS

Blood Leucocyte Count.—Adequate study of the course of the leucocyte response was not made in any of these cases, and in nine of them there was no count recorded. The remaining 45 cases have been tabulated according to a single leucocyte count. This was the first count recorded except in the cases of patients who developed meningitis in the hospital. In these cases the count selected was the one closest in time to the demonstration of meningitis. The figures are as follows:

Leucocyte count (thousands)	5-10	10-15	15-20	20-30	30-40	over 40
Number of patients	6	9	16	7	4	3

In general the percentage of polymorphonuclears paralleled the total count. It is obvious that patients with influenzal meningitis may have either a leucopenia or a leucocytosis.

Blood Cultures.—Here again our data are fragmentary. Blood cultures were taken in the cases of twenty-four patients, and *H. influenzae* was found on one or more cultures in sixteen of them.

Other Cultures.—In the case of osteomyelitis of the tibia and in those of abscess of the extremities and of pericarditis, pure cultures of *H. influenzae* were obtained from these lesions. No attempt was made to study the antigenic relationship of these strains of *H. influenzae* to

those in the meninges. Influenza bacilli were also grown from pleural fluid in one case and from a submaxillary abscess in another. *H. influenzae* was cultured from otitic discharge in two instances, although few ear cultures were made.

Cerebrospinal Fluid.—Dynamics: Definite evidence of block was observed during life in one patient and at necropsy in another. A third patient showed a pressure cone at necropsy.

Cytology: In two cases the first lumbar puncture revealed a normal spinal fluid. In several others the cell count was quite low; in four the pleocytosis was less than 500. In one of these cases a differential count showed 80 per cent lymphocytes. This fluid showed *H. influenzae* on smear and culture. In two of the other three cases the organism was demonstrated on culture though not on smear. In most instances the spinal fluid leucocyte counts were between two and ten thousand with a high percentage of polymorphonuclears. The highest count recorded in this series was 294,000 with 97 per cent polymorphonuclears. In another case the fluid was described as "too thick to count."

Bacteriology: Stained smears of the first spinal fluid sample revealed gram-negative bacilli in all but 12 cases. In 2 of these 12 the first spinal fluid specimen was entirely normal, but the second showed organisms on direct smear. Cultures were made in 53 of the 54 cases, and *H. influenzae* was eventually demonstrated in all of them, although first cultures were negative in 2. No cultures were recorded in 1 case; however, gram-negative bacilli were seen in large numbers in this patient's spinal fluid, and there is a decided probability that they were influenza bacilli. Another case, in which gram-negative bacilli were demonstrated on smear while several cultures were negative, has been excluded, for the failure of the organism to grow on ordinary media suggested that it was not *H. influenzae*. The diagnosis of influenzal meningitis should be confirmed by culture of the spinal fluid in every instance. One cannot assume that gram-negative bacilli in the spinal fluid are always influenza bacilli. One of us has seen a case of meningitis due to a related organism with different growth requirements, and another case in which the gram-negative bacilli readily demonstrated on smear turned out to be aerobic spore-formers. In young infants, of course, *B. coli* meningitis is not uncommon, and differentiation of *B. coli* and *H. influenzae* on morphologic grounds alone is not always easy.

With regard to the interpretation of smears, two points should be stressed: first, the pleomorphism of meningeal *H. influenzae*, and second, technical difficulties in Gram staining a relatively thick film. In several of our cases the house officer who examined the first smear was not certain whether the organisms were gram-positive or gram-negative. This difficulty can be obviated only by familiarity with the Gram stain in use, and each batch of Gram stain has its own peculiarities.

DIFFERENTIAL DIAGNOSIS

The diseases most likely to be confused with influenzal meningitis are meningococcus meningitis, other forms of purulent meningitis, and tuberculous meningitis. In practically all instances bacteriologic examination of the spinal fluid is necessary to settle the diagnosis.

Meningococcus Meningitis.—Since influenzal meningitis is often apparently "primary" and tends to run a prolonged course, the clinical picture in a given instance may strongly suggest meningococcus rather than influenzal infection. While metastatic lesions may be less common in meningococcus meningitis (only one of seventy-four infants with meningococcus meningitis observed at this hospital showed such a lesion), a guess at the diagnosis of influenzal meningitis, whether on this or any other purely clinical ground, would be distinctly hazardous. Moreover, especially to an inexperienced observer, meningeal influenza bacilli may look like diplococci on smear. In cases in which organisms are not relatively abundant in the spinal fluid, an immediate differential diagnosis becomes an impossibility. Sixteen of our fifty-four patients received one or more doses of antimeningococcus serum. This procedure was entirely correct as long as the diagnosis of influenzal meningitis was not established.

Purulent Meningitis, Other Forms.—It would appear that influenzal meningitis occupies an intermediate position between meningococcal and other forms of purulent meningitis. In the case of a patient with a subacute type of meningitis who does not appear particularly toxic, the first guess would be one of meningococcus infection and the second of influenza. Pneumococcus meningitis is likely to be fulminating in character, and a spinal fluid with a low cell count and myriads of organisms is frequently observed. In streptococcus meningitis there is frequently obvious pathology in the mastoid or some other focus of infection. However, the clinical pictures are not sharply differentiated. In particular it should be remembered that pneumococcus meningitis is often apparently "primary"; that, in fact, it may be taken for meningococcus meningitis before the puncture is done; and that influenzal meningitis, as well as epidemic meningitis, may be quite fulminant in character. Here again it is clear that the diagnosis of influenzal meningitis must depend on bacteriologic study of the spinal fluid. Often the diagnosis may be strongly suggested by examination of a direct smear. However, as gram-negative bacilli are not necessarily influenza bacilli, cultures should always be made. If *H. influenzae* is obtained on blood culture, in a case of meningitis it is obviously unlikely that another organism is causing this lesion. However, as will be seen from a case to be discussed later, similar reasoning may not be justified in instances of the isolation of *H. influenzae* from other sources.

Tuberculous Meningitis.—At first sight the possibility of difficulty in differentiating tuberculous and influenzal meningitis might appear remote. That this is not the case is shown by the cases of two patients observed at this hospital.

The first patient, a white boy aged four months, has been listed in our influenzal meningitis series. He was admitted to the hospital on March 24, 1926, with the following story: The illness had begun on March 8, with crying and fever. Retraction of the head was noted on March 11. From March 15 to 21 he seemed slightly better. However, since March 21 the color had been poor. On admission he seemed listless, and there was slight opisthotonos. The left eardrum was bulging and creamy pus was obtained on paracentesis. Physical and x-ray examination of the chest revealed extensive bronchopneumonia, and the roentgenologic diagnosis was disseminated tuberculosis. The white count was 36,000. A lumbar puncture revealed clear fluid with a cell count of 80; 60 per cent of the cells were mononuclears, and smear and culture were negative. Subsequent spinal fluid specimens showed cell counts between 500 and 2,000, with approximately 90 per cent polymorphonuclears. The intradermal tuberculin test was negative to 0.1 mg. On April 5 a culture of the spinal fluid showed *H. influenzae.* The patient died on April 12, and autopsy permission could not be obtained.

The second patient was not included in this series, although the history was filed under a clinical diagnosis of influenzal meningitis. He was a white boy, aged eleven months, who had had many colds during December, 1926, and January, 1927. In February he was admitted to a hospital on account of bronchopneumonia. He improved but developed bilateral otitis. He was discharged February 28. On March 14 his physician found the chest clear although cough continued. During the next week he acquired a "cold." On March 29 a thoracentesis was done, and a few drops of thick pus were obtained. The patient ran a septic temperature. He was admitted to the St. Louis Children's Hospital on April 6. Physical examination revealed a malnourished, poorly developed boy who appeared chronically ill. The fontanel was soft. Both eardrums were bulging, and pus was obtained from each on paracentesis. The respiration was diaphragmatic. Over the right upper lobe the percussion note was flat, and the breath sounds were tubular. X-ray examination suggested the presence of a cavity. Tuberculin test (0.1 mg.) was negative. The patient was put on postural drainage. On April 19 a thoracentesis was done. As the needle entered the chest cavity, air was expelled into the syringe; 2 c.c. of thick green pus was aspirated, and culture showed *H. influenzae.* On operation, April 23, a large cavity was found with a bronchial fistula. On the next day there was rigidity of the neck and back. On April 26 a lumbar puncture showed clear spinal fluid with 17 cells, 9 of which were polymorphonuclears. The Pandy test was one plus, and culture was negative. The following day the patient looked better. On May 1 he again looked very ill. He became spastic with marked opisthotonos and died May 3. A specimen of spinal fluid obtained on the day of death showed 26 polymorphonuclears, 24 mononuclears, and 100 red blood cells. Culture was sterile. Autopsy: Anatomical diagnosis was tuberculous bronchopneumonia, right lung, miliary tuberculosis of spleen and intestines and meninges of brain. There were yellow caseous masses in the right lung, with a few large cavities, and small whitish areas were seen in the subarachnoid space. Histologic examination revealed characteristic tuberculous lesions.

In the second case the influenza bacilli cultured from the thorax were evidently secondary invaders, and a serious diagnostic blunder resulted from another assumption. In the first case it is perhaps not inconceiv-

able that the meningitis may have been primarily tuberculous, and that invasion of the meninges by *H. influenzae* may have been secondary. Since there is no necropsy material there seems no way of settling this point. In any event, these cases indicate that differential diagnosis between tuberculous and influenzal meningitis may constitute a real difficulty.

SUMMARY

On the basis of a group of 54 cases compiled from the records of the St. Louis Children's Hospital, and of a series of 500 cases gathered from reports in the literature, an attempt has been made to discuss influenzal meningitis from the point of view of the clinician rather than of the immunologist. Incidence in hospital practice, incidence by sex and age, and mortality are briefly considered. Data from history and physical examination and from laboratory findings are analyzed, and questions of diagnosis and differential diagnosis are discussed.

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ASSOCIATION OF OTITIS MEDIA AND PNEUMONIA WITH ONSET OF INFLUENZAL MENINGITIS

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CLINICAL observations indicate that in many instances the onset of influenza bacillus meningitis is not associated with noteworthy extrameningeal lesions. The fact that meningeal strains of *H. influenzae* resemble one another and differ from the ordinary respiratory strains in their cultural and serologic characteristics[1, 2, 3] and the uncertainty as to the importance of the species in respiratory infection have led to the belief that this type of meningitis must be "primary" in practically all cases. Nevertheless, recent discussions of influenzal meningitis,[3, 4] while they attribute little significance to preceding or concomitant otitis and pneumonia, indicate that such lesions are relatively common. This paper presents further data on their frequency, and the question of their significance is discussed.

In the cases of patients with meningitis, it is often difficult to decide whether other lesions are present. For example, in very toxic or comatose patients, especially infants without striking meningeal symptoms, shifting atelectasis and transmitted rhonchi may lead to a tentative diagnosis of bronchopneumonia, not justified by later examination. However, in the cases of pneumonia cited in this paper, the diagnosis was confirmed by persisting signs, and in many instances by x-ray or autopsy. Cases of doubtful or terminal pneumonia were not included. Similarly, in the case of a very sick child, especially of one with purulent meningitis, the examiner is sometimes too easily convinced that the ears look abnormal. The diagnosis of catarrhal otitis media, based only on some redness of the drum, has not seemed definite enough to warrant discussion here. The term otitis media has been applied only to cases with definite middle ear suppuration.

In a series of influenzal meningitis cases from the St. Louis Children's Hospital, preceding and concomitant otitis and pneumonia were much more frequent in infants than in older children. Of fifty-four patients, twelve were over two years of age. Only one of these showed pus in the middle ear on admission, and none had signs of pneumonia. Of the forty-two patients under two years of age, more than half had otitis or pneumonia on admission to the hospital. Although in general such lesions are common in this latter age group, this incidence seems suggestively high.

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An analysis of the cases of the forty-two infants with influenzal meningitis reveals certain features of interest. In ten of the cases signs of meningitis developed in the hospital and were preceded by pneumonia or otitis (Table I). From a critical study of the duration of

TABLE I

10 CASES IN WHICH OTITIS OR PNEUMONIA PRECEDED MENINGITIS

PATIENT	LESION PRECEDING MENINGITIS		DURATION OF ILLNESS		FROM DEMONSTRATION OF MENINGITIS DAYS	COMMENT
	PURULENT OTITIS	PNEUMONIA	FROM BEGINNING DAYS	FROM ADMISSION DAYS		
1	+	Broncho	7	2	1	First CSF negative
2	–	Lobar	15	8	1	Culture of pleural fluid *H. Influenzae* and pneumococcus
3	+	Lobar	9	5	1	Seemed "improved" second day in hospital Twitching began on fourth day
4	+	Broncho (post-pertussis)	?	4	1	CSF culture *H. influenzae* and streptococcus
5	+	Lobar	20	13	3	Vomiting and prostration first noted tenth day in hospital
6	+	Broncho	19	12	2	Mastoidectomy third day in hospital Bronchopneumonia found 3 days after operation, stiff neck 8 days after
7	+	Broncho	20	13	1	First CSF clear. Discharging ear 1 week before admission. Fever for 3 days
8	–	Broncho	16	14	3	Autopsy showed marked peribronchial thickening. Seemed quite well on fifth day in hospital
9	+	Broncho	Recovered			Sterile pleural effusion present on admission
10	+	–		49	4	Admitted to hospital for repair of spina bifida. Pus from left ear twenty-fourth day in hospital. CSF culture negative same day, later became positive

symptoms in each instance, it seems clear that in this group the other infections actually preceded the meningitis; in two the first lumbar punctures, done because of suspicious symptoms, revealed clear sterile spinal fluid, and in these there can be no doubt of the time relation of the meningitis and the extrameningeal lesion. In twelve cases the patients admitted with meningitis showed otitis or pneumonia on admission, and in two others (Nos. 23 and 24) the children admitted with signs of bronchopneumonia may well have had meningitis at the time, although lumbar punctures were not done until later (Table II). Of these 14 patients, five were admitted before the third day of their disease and four more before the end of the first week. In the cases of patients seen early in the disease, it is unlikely that an otitis or pneu-

TABLE II

OTHER PATIENTS SHOWING OTITIS OR PNEUMONIA ON ADMISSION

PATIENT	DURATION OF ILLNESS TO ADMISSION DAYS	ADMISSION FINDINGS		TOTAL DURATION OF ILLNESS DAYS	COMMENT
		OTITIS (PURULENT)	PNEUMONIA		
11	2	–	Broncho	2	Autopsy showed extensive purulent pneumonia
12	4	+	–	14	Mastoid tenderness on admission
13	10	+	–	11	
14	16	+	Broncho	34	
15	1	+	–	2	Bilateral labyrinthitis at autopsy
16	6	+	–	7	
17	14	+	–	16	
18	2	+	–	6	
19	17	+	–	31	
20	19	+	–	22	
21	5	+	–	6	
22	5	+	–	13	
23	2	–	Broncho	19	Lumbar puncture not done until tenth day
24	2	–	Broncho	14	Lumbar puncture not done until fourteenth day

monia could be classed as secondary to the meningitis. In patients seen late in the disease, of course, this point is difficult to decide. However, for purposes of comparison, it seems safe to summarize this series with the statement that the onset of meningitis was definitely preceded by pneumonia or otitis in ten cases, and may have been concomitant with such lesions in fourteen other cases. Thus out of forty-two cases there were twenty-four in which it seemed likely that the beginning of meningitis was associated with ear or pulmonary infection.

A comparison of this series with a series of cases of meningococcus infection indicated that evidence of preceding or concomitant pneumonia and otitis was significantly less common in the latter group. A series of seventy-four cases of epidemic meningitis in children under two years of age was compiled from the St. Louis Children's Hospital records. In two of these cases the meningitis was preceded by bronchopneumonia and in one case by mastoiditis. Eight other patients had otitis media on admission to the hospital with meningitis, and two of these also had bronchopneumonia. From elementary statistical considerations it appears unlikely that the higher incidence of such lesions in the influenzal meningitis series could be attributed to coincidence.[5, 6]

Although the cases of influenzal meningitis with otitis media were carefully studied in an attempt to determine whether the ear was the source of intracranial infection, data on this point were meager. Postmortem examination of seven patients who had shown purulent otitis on admission and of three others who had anatomic evidence of temporal bone involvement although there was no aural discharge during life, revealed no instance in which the meningitis could confidently be

classed as otogenic. In one case there was a pachymeningitis of undetermined duration, while in the others the dura was uninvolved. Osteomyelitis of the skull, localized temporal abscesses, and sigmoid sinus thrombosis were not found, and their absence was sometimes of considerable interest. Patient No. 1 (Table I), for example, admitted two days before death, was found to have pus in both ears and a negative spinal fluid. At necropsy a very recent influenzal meningitis was found; yet even in this case there was no evidence of temporal localization. The fact that no definite indication of an otitic source of the meningitis was found in any of these cases does not exclude such an origin. According to Alexander,[7] diffuse meningitis is the common intracranial complication of ear infection in infancy, localized processes being rarely encountered. It is possible that the ear might be the source of the meningitis in these cases, and the labyrinthitis found in two of the three instances in which serial sections of the temporal bone were made could perhaps be construed as evidence for this view. It is also possible, however, that the inner ear infection was secondary to the meningitis. Clinical histories in the cases with preceding or concomitant otitis add nothing of value to these inconclusive anatomic findings. Definite mastoid tenderness was noted in one case only, and in this case the mastoiditis could not have been much older than the meningitis.

While association between respiratory disease and the onset of influenzal meningitis is apparently more than a coincidence, present knowledge is inadequate to explain the nature of the relationship. It would be interesting to know whether influenzal organisms related to those in the meninges played any part in the development of the pneumonic or otitic lesion. Since it is generally agreed that meningeal *H. influenzae* invade the body by way of the respiratory tract and since these organisms exhibit diversified pathogenic potentialities, there is nothing inherently improbable in this hypothesis. Meningeal *H. influenzae* differ from ordinary respiratory strains in their invasiveness upon inoculation into laboratory animals, as well as in their cultural and serologic characteristics. In laboratory animals meningococci are definitely less invasive. Metastatic lesions are apparently quite common in influenzal meningitis since they were observed during life in six of our fifty-four cases. One of these patients had an osteomyelitis of the tibia, and three had abscesses of the extremities. *H. influenzae* was recovered in pure culture from all of these lesions. No cultures were made from the cellulitis which occurred in the two remaining cases. Bacteriologic study of pericarditis found at necropsy in two additional cases of influenzal meningitis revealed pure cultures of *H. influenzae*. In another instance influenza bacilli with pneumococci were recovered during life from a pleural effusion. For comparison, among the group of 74 cases of meningococcus meningitis cited in this paper, there was but one instance in which a metastatic lesion was found during life, while in

another endocarditis was discovered at necropsy. This difference between the two groups is suggestive, though not quite enough to be statistically significant, and is in accord with the impression gained from animal experiments that the meningeal influenza bacillus is a more versatile pathogen than the meningococcus. Hence the observation that the latter organism seldom damages the respiratory mucosa does not indicate that meningeal *H. influenzae* must also be harmless to this tissue. Using a strain of *H. influenzae* which may not have been related to the meningeal type, but which clearly differed from the usual strains in its invasive properties, Blake and Cecil were able to produce an experimental bronchopneumonia in monkeys.

On the basis of the hypothesis that meningeal *H. influenzae* can produce respiratory pathology, it would be interesting to look for this organism in the respiratory tracts of patients with influenzal meningitis. The recovery of ordinary *H. influenzae* would be of little significance, for it is frequently found in the respiratory tract, and its relation to meningeal strains is as dubious as its pathogenicity. Meningeal strains, however, are not often met with in the absence of meningitis, and their isolation from the respiratory tracts of two patients with influenzal meningitis is perhaps of some interest. No other reports of this sort have come to the author's attention, and little work has been done along this line since convenient technics for identification of meningeal strains have only recently been developed. In the two cases cited, the cultures may merely indicate that the organisms passed through the nasopharynx on their way to the meninges. In a case recently observed at the St. Louis Children's Hospital, the nose culture showed large numbers of influenza bacilli which proved to be serologically identical with those in the meninges. The child had an otitis media, but satisfactory ear cultures were not obtained. Meningeal *H. influenzae* has also been isolated from the nasopharynx in one case reported by Pittman. These cultures, while they show the feasibility of isolation of meningeal *H. influenzae* from the respiratory tract, offer no evidence of its importance as a respiratory pathogen. Evidence on this question would be difficult to obtain, for influenza bacilli may spread within the respiratory tract in infections due to other agents. Even the recovery of invasive influenza bacilli in pure culture from an area of pneumonic consolidation would not establish their pathogenic rôle in this lesion with certainty. However, an intensive search for meningeal *H. influenzae* in otitic and pneumonic lesions of patients with and without influenzal meningitis might lead to results of interest. Such a study might possibly help to clarify our general concepts of the pathogenic activity of influenza bacilli.

Since in the cases cited, there is no proof that influenza bacilli took part in the induction of the respiratory lesions, two other hypotheses suggest themselves, both of which assume that these lesions are caused

by other agents. According to the first hypothesis, changes in the respiratory mucosa may facilitate the passage of influenza bacilli across this membrane into the blood and meninges. A spread of influenza bacilli within the respiratory tract, such as is seen in a variety of infections, might, if the influenza bacilli were potentially virulent, contribute to the development of generalized *H. influenzae* infection. The second hypothesis disregards local tissue changes, and assumes that a constitutional susceptibility to *H. influenzae* infection might be induced by respiratory disease. However, at the present time discussion of these or other hypotheses would be purely speculative.

To conclude, association between respiratory disease and the onset of influenzal meningitis is more than a coincidence, since analysis of the experience at this institution showed preceding and concomitant otitis and pneumonia to be significantly more common in a group of infants with influenzal meningitis than in a similar group with meningococcus meningitis. However, the nature of the relationship between respiratory infection and influenzal meningitis cannot be determined at present since there are no cogent data available.

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THE TREATMENT OF INFLUENZAL MENINGITIS WITH IMMUNE SERUM

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INFLUENZA bacillus meningitis is one of the commoner infections of the central nervous system. In the experience of Neal[1] *H. influenzae* ranked fourth as a cause of purulent meningitis. The figures for the St. Louis Children's Hospital from 1918 to 1935, as shown in the accompanying tabulation, give a similar impression.

Meningococcus meningitis	160 cases
Streptococcus meningitis	74 cases
Pneumococcus meningitis	62 cases
Influenza bacillus meningitis	54 cases
Staphylococcus meningitis	24 cases

Since influenzal meningitis is relatively common and since the mortality is high, it was logical to investigate the possibility of treatment with immune serum. Ordinary respiratory strains of *H. influenzae* exhibit a marked antigenic heterogenicity, i.e., a serum made from one strain will probably show little or no reaction with the next strain tested, but the close antigenic relationship exhibited by meningeal strains[2, 3] might encourage hopes for the development of an immune serum which would be therapeutically effective in infections due to those strains.

In interpreting the reports of cases of influenzal meningitis in which recovery was associated with the use of serum, it is important to remember that recovery was not unknown before the introduction of serum. Moreover, while the prognosis is always poor, recovery is more frequent in patients over two years of age than in infants. Our own experience includes 39 cases in which no serum was used. Nine of these cases were in children over two years of age, and in this group there were two recoveries, while of the 30 infants only one recovered. A critical survey of the individual reports of 500 cases of influenzal meningitis from the literature was made by one of us (D.W.W.), including only those in which the diagnosis seemed certain. Although this series included 10 patients treated with serum with 1 recovery, it can be considered as a satisfactory control group. There were 373 infants under two

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years of age with 9 recoveries, giving a mortality of 97.6 per cent, while 26 of the 127 patients over two recovered, or a mortality of 79.5 per cent. This series of unselected cases illustrates the higher incidence of the disease as well as the higher mortality in infancy.

The literature contains but few papers on serum treatment of influenzal meningitis. From the very paucity of such reports, one might assume that the results had been as disappointing as the few available data would indicate. Ward and Wright[4] have reported on eight cases with one recovery. Recovery occurred in one of Pittman's 18 cases. Our own material includes 15 patients treated at this hospital and 4 treated elsewhere. One of these patients recovered, a boy aged seven years, under the care of Dr. John A. Kolmer. Kuttner's patient (reported by Ward and Wright) was also more than two years old. One would have been more inclined to attach significance to these recoveries if the individuals had been infants. If these patients had been the only ones in the older age group who had received serum, a stubborn optimist, while conceding that the serum was perhaps useless in infants, might have continued to hope that it would be useful in older patients. However, 6 of our 16 treated patients were more than two years old. The age is given in but 10 of the other recorded cases, and in 6 of these it was more than two years. Evidently the ultimate results are discouraging in both age groups.

A temporary sterilization of the spinal fluid was noted in 5 of Ward and Wright's cases, in 3 of Pittman's, and in 2 of our own. Before the introduction of serum treatment, little attention was paid to the spinal fluid after the diagnosis had been made, and our material does not enable us to determine whether such a temporary sterilization may occur spontaneously. Since the course of the disease often tends to be somewhat prolonged and since recovery from influenzal meningitis was not unknown before the introduction of immune serum, it may well be that such sterilization occurs spontaneously.

The possibility that the poor results cited here may be attributable in part to the age of the patients and to delay in the institution of treatment immediately suggests itself and cannot be excluded. However, among 74 children with meningococcus meningitis observed in this hospital whose ages were under two years, there were only 31 deaths, and many of the patients who recovered were not treated until late in the disease. Hence it does not seem that either of these factors can altogether account for the apparent failure of serum treatment in influenzal meningitis.

Neal[1] has mentioned the possibility of the development of a more effective serum. However, an exhaustive analysis of the antigenic structure of *H. influenzae* has already been made by Pittman and by Ward and his coworkers, and the serums used by them seem theoretically ade-

quate from our present knowledge. Serum of the same type was used in six of our cases. Although we do not feel hopeful about the improvement of serum therapy in influenzal meningitis, we believe that any further work along this line must take account of the experimental studies just mentioned, and it seems desirable to accord them a brief review.

Freshly isolated strains of meningeal *H. influenzae* exhibit many salient characteristics by which they differ from most strains from other sources. A capsular structure is present; growth on suitable media is mucoid in character; and the organisms are invasive upon inoculation into laboratory animals. Supranatant fluid from a centrifuged culture will produce a precipitin reaction in suitable serum, thereby demonstrating the presence of a soluble antigen. A close correlation exists among all these properties, and all may be rapidly lost on subculture unless due precautions are taken. Pittman has shown that nearly all strains of meningeal *H. influenzae* possess the same type of soluble antigen. This specific soluble substance, or S-substance, is apparently not the entire explanation of the serologic homogenicity of this group of organisms since serum prepared from old cultures which have lost this component may agglutinate both old and fresh strains. However, there is considerable evidence to suggest the importance of this S-substance in influenza bacillus infections.

The observations of Ward and Wright[4] indicate that this S-substance possesses the property of protecting influenza bacilli from the bactericidal action of serum of normal animals and that, if a test strain is well endowed with S-antigen, significant bactericidal activity is shown only by immune serum containing S-antibody and is closely correlated with the concentration of this antibody. Serum prepared from old strains which had lost the S-antigen agglutinated freshly isolated strains but had little or no bactericidal power against them. Similar observations are recorded by Weiss.[7]

Data on pneumococcal structure and immunity provide a close analogy to the observations recorded for meningeal *H. influenzae*. In pneumococcus infections, it appears that an S-antigen-antibody reaction is of considerable importance in determining the course of the disease, while antibody for another antigenic component of the pneumococcus may cause agglutination of the organisms in vitro, while conferring little if any benefit on an infected host.[5, 6] Some of Weiss'[7] observations on experimental infection of rabbits with virulent *H. influenzae* might suggest that serums with relatively little S-substance showed some tendency to retard the progress of the infection. There is, however, little theoretical justification for the clinical use of such serums. Nine of our patients were treated with a serum of this sort, and no evidence of beneficial effect was noted. In four of our case histories the nature of the serum used was not recorded, so that in six cases only can one be cer-

tain that the serum used contained S-antibody. The one recovery occurred in this group. However, in all the cases reported by Pittman and by Ward and Wright, the serum used contained S-antibody, and such serum apparently offers little hope for improvement in the ultimate prognosis.

On the basis of experimental data, Ward and his colleagues believe that fresh human serum should be added to immune serum in the treatment of influenzal meningitis. This procedure, based on the demonstrated absence of complement in the spinal fluid of influenzal meningitis and the apparent necessity for complement in bacteriolysis, was carried out in all their cases and in all of ours. However, in the case of recovery reported by Pittman, the spinal fluid became sterile after two treatments with immune serum alone, and two of the three patients who showed temporary sterilization of the spinal fluid received no fresh complement added to the serum. Nevertheless, theoretically the addition of active serum seems indicated.

Although in the reported cases the treatment has not been as uniform as might be desired for an optimum clinical experiment, the published data indicate quite clearly that despite much study of the rationale and mechanics of the procedure, treatment with immune serum offers little hope for the patient with influenzal meningitis. These discouraging results are not altogether surprising, for although a variety of clinical infections have been treated with *antibacterial* serums, in general the results have been disappointing. Antimeningococcus serum and Type I pneumococcus serum are perhaps the only well-established exceptions to this statement. The usefulness of the latter is restricted within sharp if ill-understood limits since it seems to be quite ineffective in the treatment of purulent processes and specifically of meningitis, due to pneumococcus Type I. It is remarkable that so far no serum with a clinical effect remotely resembling that of antimeningococcus serum has been discovered. The analogies between influenzal and meningococcus meningeal infections would make it appear possible to produce an effective antiserum for influenzal meningitis. However, anti-influenzal serum is not a success despite the brilliant and arduous work which lies back of some of the clinical experiments which we have discussed. Clearly there is some unknown factor which makes the dislodgment of the meningococcus relatively easy, while meningeal *H. influenzae* is not readily evicted.

In conclusion, it may be stated that the results of serum treatment of influenzal meningitis have been discouraging, and that there is no obvious justification for optimism as to the possibilities of future work. The use of such serum is purely experimental, and its commercial exploitation seems quite unjustified. If investigation of serum treatment is to be continued, the serum should contain anti-S-substance, since there

is little theoretical justification for the use of serum devoid of this component. Active human serum should probably be added to the immune serum, though one can only guess at the optimum proportions. Furthermore, the organism should be typed in every case. There seems no justification whatever for continuing this mode of therapy unless such stipulations are fulfilled.

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A FOLLOW-UP STUDY OF AMBULATORY CHILDREN WITH TUBERCULOSIS INFECTION

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THIS study was undertaken to determine the course of tuberculous infections in ambulatory children. The majority of follow-up reports deals with sanitarium cases of childhood tuberculosis and offers no comparison for this group. Many statistical studies of school surveys have disclosed the incidence of tuberculous infection in apparently healthy children. However, these individuals have not been observed for a sufficient length of time to know their ultimate fate. An attempt is made to answer this last question from an analysis of the subsequent data.

Our material originally consisted of 639 children who attended the out-patient children's chest clinic at the University of California Hospital. They were referred from the general pediatric clinic because of exposure to tuberculosis or as tuberculous suspects. Only 162 patients returned for the final recheck. All cases were tested by the Mantoux method with 0.1 mg. of old tuberculin. Complete physical and x-ray examinations were performed at the initial visit and at intervals thereafter. At the initial examination two children had negative tuberculin tests but were included here because of definite roentgen evidence of tuberculous infection. A brief summary of the records of these two patients is as follows:

CASE 1.—H. B., a male eleven years of age, had had no history of contact but was brought to the clinic because of cough and night sweats for three months. There were no abnormal physical findings, but the x-ray plates showed calcified hilar glands. At reexamination, eight years later, the patient was perfectly well. The tuberculin test was still negative; there were no physical signs, and the roentgen picture was unchanged.

CASE 2.—H. A., a six and one-half-year-old female child, was brought in because of malnutrition. There was no definite history of exposure. Physical examination was essentially negative, but x-ray pictures revealed hilar gland calcification. Ten years later the patient was perfectly well with no physical evidence of tuberculosis. The tuberculin test was again negative, and the x-ray picture unchanged.

The division into age groups and the number of years these cases have been followed is shown in Table I. Sixty-four per cent were observed for more than six years.

The sources of infection are illustrated in Table II. Over two-thirds gave a definite history of exposure, and of these patients 89 per cent were exposed to members in the same household.

From the Pediatric Department of the University of California Medical School.

TABLE I

UNIVERSITY OF CALIFORNIA CHILDREN'S CHEST CLINIC FOLLOW-UP RECORD

INITIAL AGE (YEARS)	NUMBER OF CASES	NUMBER OF YEARS FOLLOWED				
		(3-5)	(6-8)	(9-11)	(12 AND OVER)	AVERAGE
0- 4	54	22	18	11	3	6.6
5- 9	73	26	21	20	6	7.2
10-15	35	10	13	10	2	7.0
Total = 162 Males = 88 Females = 74		58	52	41	11	

TABLE II

SOURCE OF INFECTION

AGE YEARS	INTRA-FAMILIAL	INTRADOM-ICILIARY	EXTRADOM-ICILIARY	MILK	NEGATIVE
0- 4	30	6	3	1	14
5- 9	37	3	6	0	27
10-15	20	3	1	1	10
Total	87	12	10	2	51

Exposed = 68%
No History of Exposure = 32%

A comparison of the clinical and roentgenologic findings at the onset with those after the follow-up period is given in Table III. It is quite evident that the incidence of symptoms and physical signs is materially decreased at the final examination.

TABLE III

COMPARISON OF CLINICAL AND ROENTGEN FINDINGS

SYMPTOMS	ONSET		RECHECK	
	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
	67	41	8	5
Physical signs	68	42	32	20
Roentgen findings				
Negative	68	42	68	42
Doubtful	50	31	12	8
Latent	25	15	79	49
Active	19	12	3 (1 death)	2

The chest roentgenograms have been classified as follows:

a. Negative—no evidence of tuberculous infection.
b. Doubtful—enlarged hilar shadows but no other tuberculous manifestations.
c. Latent—including focal calcification of the lung, parenchymal fibrosis, hilar gland calcification, and pleural calcification.
d. Active—infiltration and cavitation of the lung tissue.

Seventy-three per cent of the initial x-ray examinations were either negative or doubtful. The percentage of latent cases increased from

15 per cent initially to 49 per cent at the final recheck. This increase was due to the change of the doubtful and active groups to a latent stage. Only 2 per cent were active, whereas originally 12 per cent had been so.

The x-ray changes for the different age groups are analyzed in Chart 1. The doubtful cases are grouped with the negative ones. In all age divisions the initial negative cases remained so or finally showed evidence of a latent process but did not develop changes of active tuberculosis with the exception of one individual in the 0-4 year group. Those patients showing latent tuberculosis at the initial examination were found to be latent at the final recheck in all age sections. The group with active tuberculosis initially became latent with the exception of four cases. Two of the latter became negative while two remained active. In our 10-14 year age division no activation of the pulmonary

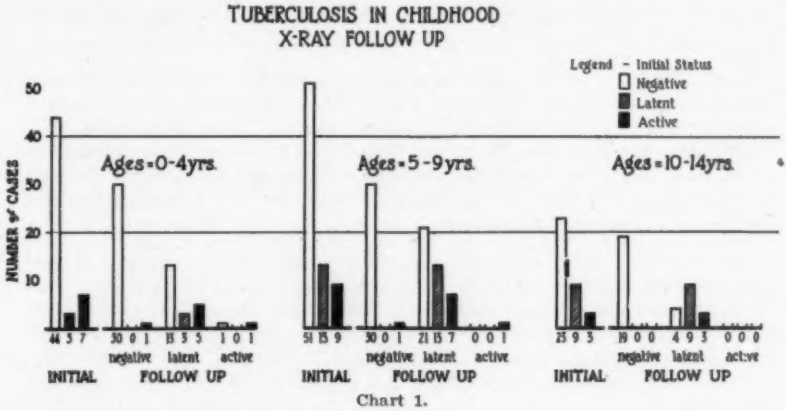

Chart 1.

tuberculous infection was shown by roentgenogram. One patient who initially had had infiltration of the right apex at the age of thirteen years now, after four years of observation, showed parenchymal fibrosis and hilar gland calcification. However, there was an active tuberculous process in the lumbar vertebrae.

The interval history reveals that 30 patients (18.5 per cent) required sanitarium care; 10 were in the 0-4 age limit, 15 in the 5-9 year group, and 5 in the oldest age group. One patient in the youngest division died of tuberculous meningitis, the only death in this series. Examination of the death certificates of San Francisco for the whole period of this study revealed only one death from tuberculosis in the remaining 477 cases of the original group of 639 children. This is strong supportive evidence that our assumption that the mortality rate from primary tuberculous infection in ambulatory children is extremely low is correct. Only two patients at present have active pulmonary lesions.

Austrian,[1] who observed dispensary children for a period of eight to twelve years, concluded that the number of young individuals exposed to tuberculous infection who develop tuberculous disease is relatively small provided contact with the infecting source is abolished when its existence has been established and provided ordinarily good hygienic and dietetic regimens are maintained. In only eight patients of the whole group was the exposure continued, and the active and fatal cases described previously were all in this group. This study again illustrates the well-known fact that reinfection from continued exposure is responsible for the activation of tuberculous processes in childhood.[2]

One of the striking features in this study was the loss or diminution of skin sensitivity to tuberculin manifested by four patients. Initially positive to 0.1 mg. of old tuberculin, three were negative on recheck to dilutions up to 10 mg., while one did not react to 0.1 mg. but was not tested with stronger solutions. A varying sensitization to tuberculin has been previously recorded.[1, 2] A brief résumé of the preceding cases is appended:

CASE 1.—A. E., a white female, six years of age, was first seen because of cough and lassitude. She had had no known exposure. Physical examination revealed râles at the left apex and the roentgenogram showed enlarged bronchial glands and increased parenchymal markings in the left upper lobe. At recheck, eleven years later, she was well except for intermittent asthmatic attacks. The roentgen ray examination showed calcified nodes at the tracheal bifurcation. The tuberculin test was negative to 0.1 mg. of old tuberculin.

CASE 2.—A. T., an eleven-year-old white female, had no history of exposure. Her symptoms were anorexia, failure to gain, and fatigability. Physically there were no positive findings and x-ray examination showed only increased bronchial markings. Reexamination at twenty-one years of age, two years after marriage, showed a well-developed individual with no abnormal physical signs or x-ray changes. Her tuberculin test proved to be negative with a dilution of 10 mg. of old tuberculin intradermally.

CASE 3.—B. B., a female child of five years, had been exposed over a four months' period to the grandfather who had active pulmonary tuberculosis. She had no complaints, and physical and x-ray examinations were negative. Five years later the patient was still perfectly well, and the status was unchanged clinically and roentgenologically. Exposure had been discontinued. The Mantoux reaction was negative up to 10 mg. of old tuberculin.

CASE 4.—J. O., a female child, was first seen at the age of seven years with symptoms of anorexia, fatigability, and listlessness. Physical examination was negative. The roentgenogram revealed enlarged bronchial glands. In the interval between the initial and final visit at seventeen years of age the patient had been in a sanitarium for eight months. At the last check-up she was symptom-free and without physical signs or positive x-ray findings. Her skin test was negative with 10 mg. of old tuberculin intracutaneously.

SUMMARY

One hundred and sixty-two ambulatory children with pulmonary tuberculous infection were followed over an average period of approxi-

mately seven years. Initial and subsequent studies included tuberculin testing and complete physical and roentgenologic examinations.

Clinically all patients, with four exceptions, are now perfectly healthy. These latter cases belong in the group of eight, in which exposure continued. In the whole series there was but one death; this caused by tuberculous meningitis occurred in the 0-4 year division.

The roentgen ray findings became negative or latent in 98 per cent of all cases. The 12 per cent initially active lesions diminished to 2 per cent at the last recheck. The majority of patients with doubtful x-ray shadows at the commencement later revealed evidence of latent tuberculous processes.

Four patients initially positive to 0.1 mg. of old tuberculin intradermally showed altered skin sensitivity on follow-up. Three were negative to old tuberculin in dilution up to 10 mg. and have always had negative chest plates. One individual did not react to 0.1 mg. of tuberculin but could not be tested with stronger dilutions. Her roentgenogram revealed calcification at the tracheal bifurcation.

CONCLUSION

The subsequent course of ambulatory children with pulmonary tuberculous infection is extremely favorable provided that they are adequately supervised and are not exposed to reinfection.

We appreciate gratefully the thoughtful cooperation of Miss Dorothy Keane and Mrs. Hazel Leseque of the Children's Out-Patient Department of the University of California in the preparation of the material for this paper.

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450 SUTTER STREET

HYPERPYREXIA OF SIXTEEN MONTHS' DURATION OF UNKNOWN ETIOLOGY

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IN THIS communication we report the case of a boy eight years old who has had a continuous elevation of temperature of unknown origin for over sixteen months.

S. R., male, eight years old, was admitted to the Israel Zion Hospital of Brooklyn, N. Y., on Nov. 4, 1934, because of fever and pain in the right leg of six days' duration. The onset occurred with hyperesthesia which increased to such a degree that even the bed sheet could not be endured, and, in addition, there was severe pain in the right leg, prohibiting all motion. For six days before admission the temperature ranged from 101° to 102° F. Because of the hyperesthesia, the elevation of temperature, and the inability to move the right limb, a diagnosis of poliomyelitis was made by the family physician, and a lumbar puncture was done before the child was admitted to the hospital. Examination of the fluid showed ten cells—all lymphocytes.

We saw the child for the first time on the day he was admitted to the hospital. Examination at that time revealed the following: the temperature was elevated to 104.2° F.; the patient, however, did not appear particularly ill; marked diffuse tenderness was present in both lower extremities and the boy seemed to be unable to move his right leg; the knee jerks were absent; there was no rigidity of the neck; but rigidity of the back was present; the cremasteric and abdominal reflexes were normal, and the Babinski sign was absent; there was no swelling or tenderness about the joints. The remainder of the physical examination was negative. On admission the white blood count was 24,900, of which 87 per cent were polymorphonuclear leucocytes, 12 per cent lymphocytes, and 1 per cent eosinophiles; the red blood count was 4,728,000; the hemoglobin (Sahli) was 73 per cent. The urinalysis was negative. Lumbar puncture was done and 10 c.c. of clear fluid was removed for examination; there were 100 cells, practically all lymphocytes, in 1 c.mm. of fluid. All the subsequent laboratory data are given in Tables I and II.

Because of the absent knee jerks and the pleocytosis in the spinal fluid, a diagnosis of acute poliomyelitis with an involvement of both lower extremities was entertained and a transfusion of 400 c.c. of whole blood from an immune donor was given intravenously. The temperature, however, continued to remain elevated and fluctuated daily between 100° and 106° F. Two days later, because of the septic temperature and because of an almost immediate and complete return of motion in the

From the pediatric service of the Israel Zion Hospital.

right leg, the diagnosis of poliomyelitis was discarded. It is difficult to explain the pleocytosis in the spinal fluid on the second puncture, but we believe that the increase in the number of cells may have been due to an irritation of the meninges caused by the first lumbar puncture done at home. The knee jerks became active again six days after admission. We have no explanation for their absence early in the disease.

TABLE I

LABORATORY DATA—BLOOD STUDY

Hemoglobin and Cell Count

DATE	HEMOGLOBIN (SAHLI)	R.B.C.	W.B.C.	P.	L.	E.	B.	M.	SMEAR
11/ 3/34	73%	4,728,000	24,900	87	12	1			Neg.
11/ 7/34	85%	5,000,000	15,900	87	11	2			Neg.
11/16/34	75%	3,700,000	16,200	75	22			3	Neg.
11/23/34	91%	4,800,000	22,100	92	4	1	1	2	Neg.
11/29/34	75%	4,792,000	23,800	95	5				Neg.
12/17/34	90%	5,250,000	41,200	91	7			2	Neg.
2/ 7/35	78%	4,250,000	22,400	87	12			1	Neg.
3/ 7/35	65%	3,400,000	18,600	83	10	3		4	Neg.
5/22/35	76%	4,200,000	15,700	82	14			4	Neg.

Blood Culture

DATE	RESULT
11/ 6/34	Positive culture *(Streptococcus hemolyticus)*
11/ 6/34	No growth
11/16/34	No growth
12/ 3/34	No growth
1/ 3/35	No growth
1/25/35	No growth
2/ 6/35	No growth
2/12/35	No growth (Aerobic and anaerobic cultures)
5/21/35	No growth

Serology

DATE	TEST	RESULT
11/23/34	Wassermann and Rosenthal	Negative
11/23/34	Widal for typhoid and paratyphoid	Negative
12/17/34	Agglutination for melitensis abortus	Negative
2/15/35	Agglutination for melitensis abortus	Negative
3/ 1/35	Mouse test for *Spirocheta morsus muris*	Negative
3/15/35	Mouse test for *Spirocheta morsus muris*	Negative

Chemistry

DATE	GLUCOSE	UREA NITROGEN	CREATININE	URIC ACID
11/23/34	94.8 mg. %	16.8 mg. %	1.49 mg. %	4.06 mg. %

Sedimentation Rate

DATE	WESTERGREN INDEX
5/21/35	64.6 (normal 12-15)

A blood culture taken on November 6 at 11:45 A.M. revealed the presence of hemolytic streptococci, but, unfortunately, no report of the number of colonies was made. A second culture taken on the same day at 9 P.M., after the child's temperature had fallen precipitately to 96° F., showed no growth, and every subsequent culture taken over a period of nine months, anaerobic as well as aerobic, was consistently negative (Table II). For a time, however, the case was considered one of sep-

ticemia because of the single positive blood culture, but every effort to find a focus of infection was futile. Finally, on Feb. 15, 1935, the diagnosis of sepsis, too, was discarded because of the repeated negative blood cultures. During this time nine transfusions of 200 to 250 c.c. of whole blood each were given intravenously at irregular intervals.

TABLE II

ADDITIONAL LABORATORY DATA

Spinal Fluid

DATE	APPEARANCE	PRESSURE	CELLS	ALBUMIN	GLOBULIN	GLUCOSE
11/3/34	Clear	Normal	10	--	--	--
11/4/34	Hazy	Normal	100 (lymphocytes)	2 plus	Absent	Present

N.B. First tap was done at patient's home on day before admission.

Urine

Examinations were made every 3-5 days during entire hospital stay. Only findings were those of a febrile urine (e.g., an occasional pus cell and hyaline cast).

Tuberculin Tests

DATE	TEST	CONCENTRATION	RESULT
11/ 6/34	Mantoux	0.1 c.c. 1-1,000 O.T.	Negative
11/13/34	Mantoux	0.1 c.c. 1- 100 O.T.	Negative
11/20/34	Mantoux	0.1 c.c. 1- 10 O.T.	Negative

Electrocardiographic Studies

DATE	RESULT
1/10/35	Normal tracing
4/16/35	Normal tracing
3/ 7/36	Normal tracing

Roentgenographic Studies

DATE	AREA EXAMINED	FINDINGS
11/ 9/34	Dorsolumbar spine	Normal
11/ 9/34	Pelvis	Normal
11/12/34	Pelvis	Normal
11/18/34	Sinuses	Normal
11/19/34	Pelvis	Normal
11/23/34	Chest	Normal
11/30/34	Mastoids	Normal
2/26/35	Pelvis	Normal
3/ 6/35	Dorsolumbar spine	Normal

N.B. Since discharge from hospital repeated fluoroscopic examinations of the heart and lungs failed to reveal any abnormal findings.

On Nov. 9, 1934, tenderness was present over the upper and outer aspect of the right thigh; rectal examination also revealed an area of tenderness about the left pubic bone near the ischium, but subsequent observation and repeated roentgen ray examinations of the pelvis and of both femurs failed to show the presence of any osseous pathologic changes. Similarly, repeated roentgen ray studies of the lumbodorsal spine and pelvis at intervals of several weeks failed to disclose any evidence of skeletal infection. The generalized hyperesthesia gradually subsided, but the elevation of temperature continued with a fluctuation of six to eight degrees in twenty-four hours.

From Nov. 4, 1934, the day of admission, until March 25, 1935, there was a daily fluctuation of temperature from 99° to 106° F., a difference of 7°. On March 25 and 27 there was no elevation of temperature for the first time. On March 28 the temperature again began to rise but did not reach the previous levels daily although on many occasions the temperature rose to 105° F. This continued until June 2, approximately seven months after the onset of the disease, when the temperature curve became irregular and, although many days followed in which fluctuations of five degrees still occurred, there were days when only a slight rise was observed. As time went on, the number of days when little or no elevation of temperature occurred increased until fever-free intervals of three and four days were quite common. During the last week of the child's stay in the hospital (July 17 to 23) the highest temperature was 101° F. (Chart 1). Elevations to 103° F. and even 104.5° F., however, occurred for a few hours every four to five days during August. During September the highest temperature noted was 103° F. and the longest fever-free interval was six days; and thus the tendency to subsidence continued so that the elevations became fewer and lower until finally, in January, 1936, the highest temperature observed was 101° F. and the longest fever-free interval was two weeks. The child had only two distinct chills; one on November 16 and the other on December 9. In both instances the chill ushered in a sharp rise in temperature.

On November 10, six days after admission to the hospital, a maculopapular eruption appeared on the posterior aspects of the left thigh and left buttock. It resembled the rash seen in serum sickness, but it was nonpruritic. After a few days it began to fade, and in two weeks it disappeared completely. The rash reappeared in two to three weeks, however, and continued to come and go for approximately fourteen months. At times the distribution resembled that of the erythema annulare encountered in rheumatic fever, that is, it appeared over the buttocks, on the extensive surfaces of the arms and legs, and occasionally on the chest; at other times it was more generalized and also involved the trunk; often it was a bright red and then again a pale pink. Several times the rash resembled measles so closely in its appearance and distribution that, were it not for the absence of Koplik spots and catarrhal symptoms, the rash could easily have been mistaken for that of measles. On April 14 the eruption was present on the abdomen and thighs and looked like urticaria.

Interestingly enough, in spite of the marked elevation of temperature over a long period of time, the child never looked dangerously ill; indeed, he was at all times bright, alert, cheerful, and cooperative.

As already stated, after Feb. 15, 1935, the diagnosis of septicemia was discarded, and a renewed search for the cause of the fever was made. The child was carefully studied for tuberculosis, malaria, sinus and

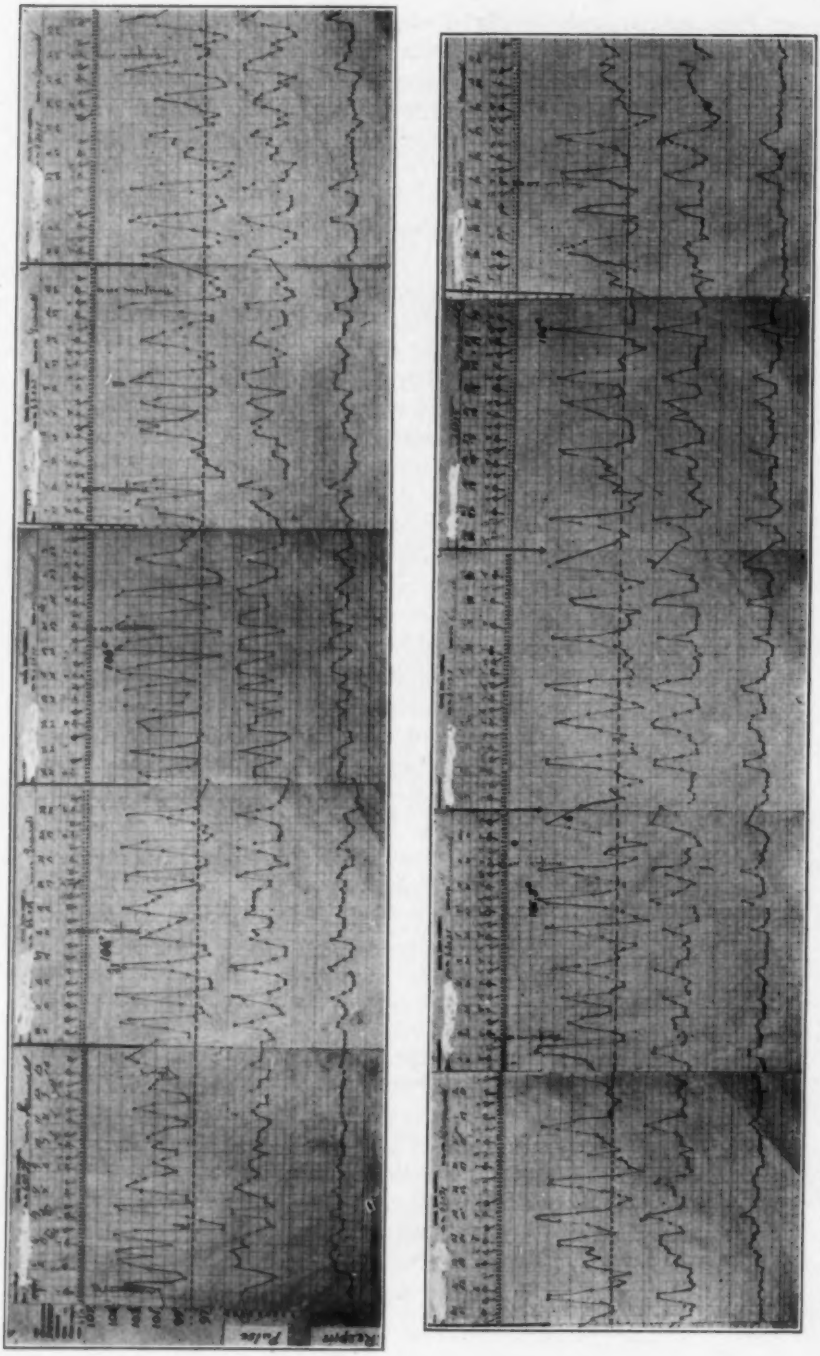

Chart 1.—The temperature curve during the patient's stay in the hospital. The heavy lines at the top of the chart indicate the weekly periods.

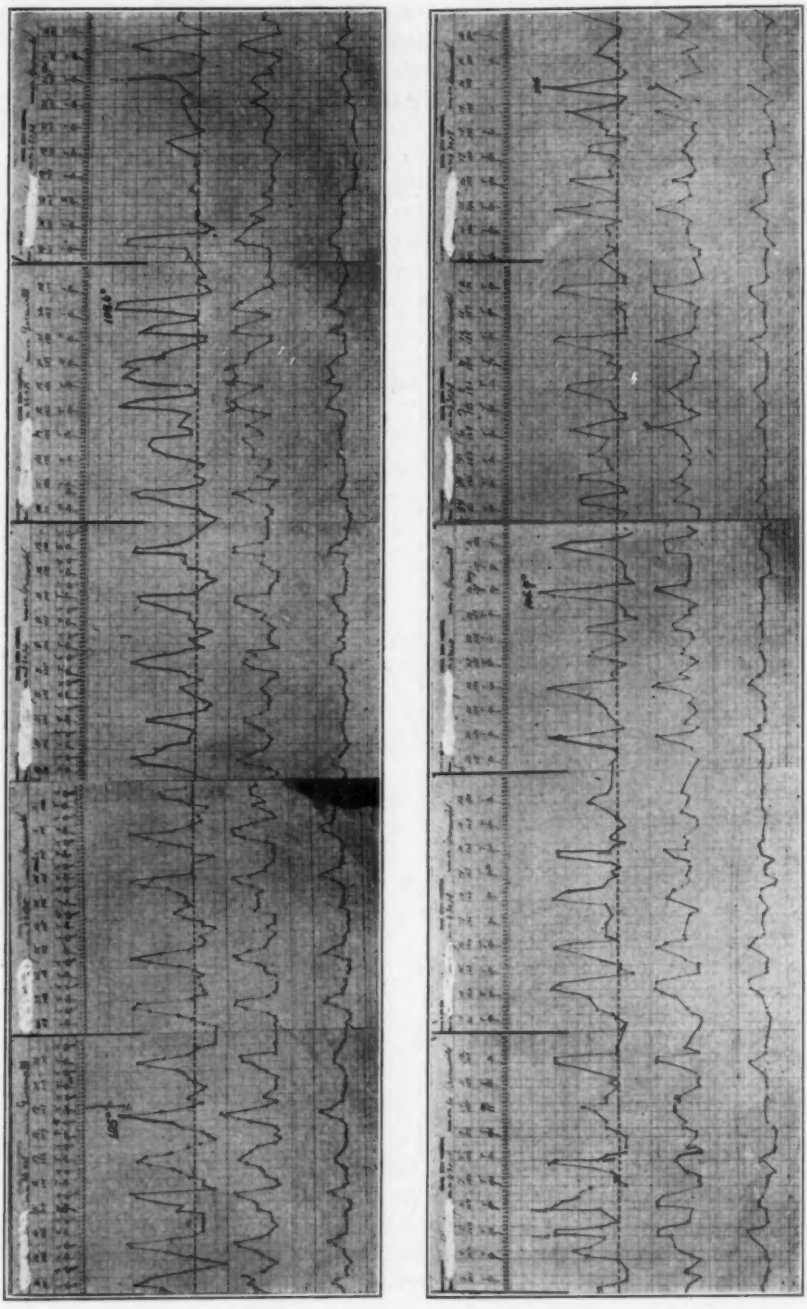

Chart 1 (Cont'd).

mastoid infection, ratbite fever, leucemia, Hodgkin's disease, rheumatic fever, syphilis, disease of the genitourinary tract, and subacute bacterial endocarditis (Tables I and II). The reasons for excluding these conditions as a cause of the fever will be discussed later.

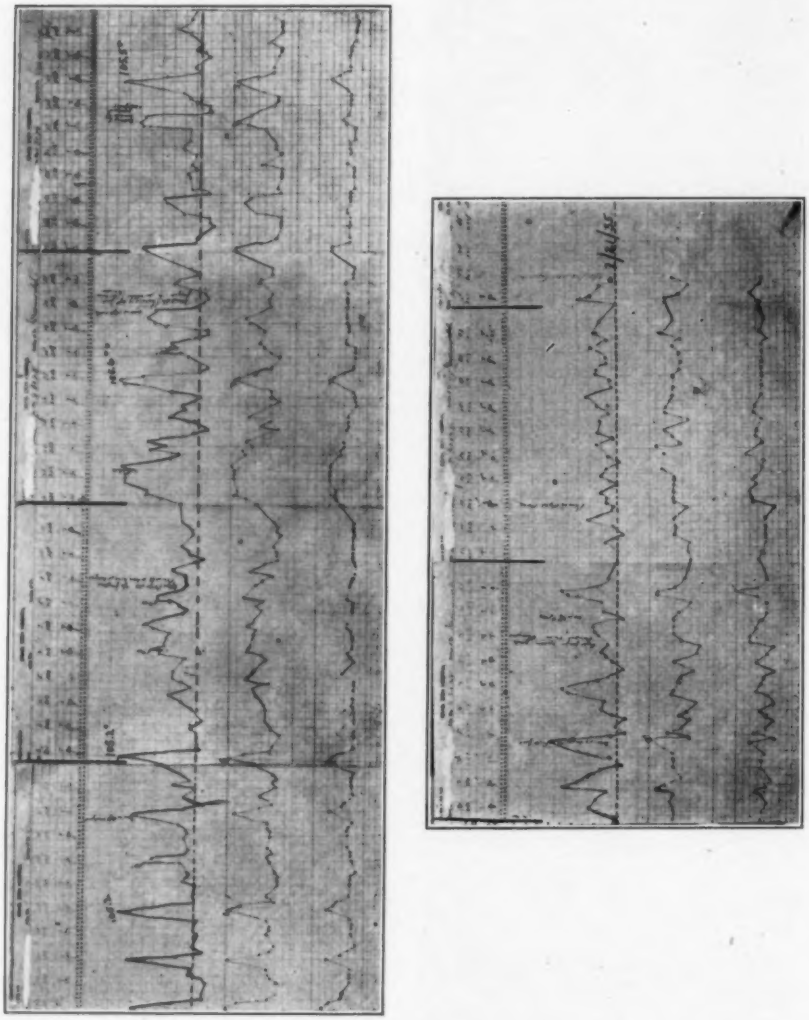

Chart 1 (Cont'd).

Fleeting joint pains appeared from time to time; thus, on November 12, he complained of pain in the right hip, and noticed limitation of motion. These symptoms disappeared after a few days but reappeared at irregular intervals involving different joints. For example, on April 20, 1935,

pain and tenderness in the interphalangeal joints of the right thumb were present for four days; on May 20 the left wrist was involved; on June 20 the left ankle, as well as the interphalangeal joints of the left forefinger, became swollen and painful; on July 9 there was pain and swelling of the interphalangeal joints of the right second finger; on July 10 the left knee and on July 14 the right knee became tender and painful. In August the cervical vertebral joints became affected with the development of torticollis which lasted about twelve weeks. Apparently, as time went on, the joint manifestations became more pronounced and seemed to reach a peak about September, 1935. The increase in the joint manifestations seemed to coincide with the subsidence of the fever. In other words, it appeared that, as the fever-free intervals increased, the joint involvements simultaneously became more frequent and prominent. Limitation of motion in the involved joints persisted long after the swelling and tenderness had disappeared. We have described the joint manifestations in some detail because the course of this patient's illness so closely resembled that of Bilderback's patient. In the description of his patient's illness, Bilderback[3] stated "after eighteen months of almost continuous fever, marked with wide fluctuations, sometimes with a variation of nine degrees in twelve hours, the patient began to show unmistakable evidence of chronic infectious arthritis."

In our case rheumatic fever was considered but ruled out because of the prolonged course without clinical evidence of cardiac involvement and because repeated teleroentgenograms of the heart failed to show any enlargement or change in configuration. At no time did repeated electrocardiographic studies show any evidence of myocardial damage. The sedimentation rate was high (Table I), but we feel that, while this is of definite prognostic value, it is of little diagnostic value in rheumatic fever.

After nine months, July, 1935, no diagnosis could be made, in spite of all efforts. As may be seen from the temperature chart, however, the fever showed a tendency to subside although fluctuations of five and six degrees in one day still occasionally occurred. On July 23 the child was discharged from the hospital and was kept under observation at home. His fever gradually disappeared. The temperature-free intervals increased from one or two days to four and five days, then to a week and finally to two weeks until, in February, 1936, a period of one month went by with only a single elevation of temperature to 102° F. The joint manifestations are still present (April, 1936) although not as severe as six months before.

Early during his stay in the hospital the patient was given frequent transfusions; later these were discontinued and amidopyrin and sodium salicylate in fairly large doses were given. These drugs were apparently without influence on the temperature or joint involvement. From the onset of the disease the child was given a full diet; special efforts were

made to see that a sufficient amount of the accessory food substances was ingested. His weight on discharge from the hospital was almost exactly what it was on admission, 73 pounds. During his stay at home the child gained weight rapidly and at the last examination on April 20, 1936, he weighed 95 pounds.

COMMENT

In the last few years several papers on fever of unknown origin have been published.[1] These papers dealt with the cases of children who had an obscure fever for periods varying from one to several weeks. In practically every case careful clinical laboratory studies revealed the diagnosis, and it was found that tuberculosis, rheumatic fever, undulant fever, syphilis, Hodgkin's disease, leucemia, sinus infection, typhoid fever, infection of the genitourinary tract including perinephric abscess, subdiaphragmatic abscess, septicemia, or subacute bacterial endocarditis was responsible for the elevation of temperature. On the other hand, reports in which fever was of more than one year's duration and in which the diagnosis remained in doubt, in spite of careful clinical and laboratory investigation, are extremely rare. As far as we know, only three cases that can be placed in this category have been thus far reported. Two of these cases were of adults who eventually developed pericarditis with cardiac enlargement, polyserositis, and glomerulonephritis with fatal termination. The diagnosis in these cases was established by necropsy studies.[2] The third case was that of Bilderback[3] who reported the case of a boy six and a half years old who had an almost continuous elevation of temperature since the age of four years. In many respects Bilderback's case closely resembles our case. For example, the age and sex of Bilderback's patient correspond with those of our patient; the duration of the temperature with the wide fluctuations; and the final development of arthritic manifestations also correspond to the signs and symptoms observed by us. It is interesting, too, that Bilderback's patient showed general hyperesthesia, a sign so prominent in our case that it led us to entertain a diagnosis of poliomyelitis.

In the differential diagnosis, rheumatic fever, tuberculosis, malaria, ratbite fever, syphilis, infection of the genitourinary tract, Hodgkin's disease, leucemia, sinus and mastoid infection, and subacute bacterial endocarditis were considered. Although the disease more closely resembled rheumatic fever than any other condition, we feel that rheumatic fever can be definitely excluded for the following reasons: First, the prolonged course of the disease was entirely unlike that of rheumatic fever; second, there was no evidence of enlargement of the heart or myocardial changes as determined by clinical, roentgen ray, and electrocardiographic studies; at no time were the cardiac sounds abnormal; third, although the joint involvement was fleeting in character, the residual stiffness and impairment of motion observed in our case after the

acute phase had subsided certainly were unlike the usual joint manifestations seen in rheumatic fever; and fourth, the marked leucocytosis in our patient was further evidence against rheumatic fever.

Tuberculosis was excluded because of the three negative Mantoux tests with increasing doses of old tuberculin. While we are aware that in rare instances active tuberculosis may be present in spite of repeated negative Mantoux tests with large doses of old tuberculin,[4] we eliminated this disease as an etiologic factor because careful clinical and roentgen ray studies of the lungs and the osseous system of our patient failed to show any evidence of tuberculosis.

Malaria was ruled out because of repeated negative blood smears and the failure to respond to quinine in large doses.

Ratbite fever was considered and discarded because of the absence of a characteristic lesion about the finger and because of the absence of the spirochete in the blood. In order to rule out this condition definitely, however, 10 c.c. of blood from the patient was injected into mice on two different occasions; examination of the blood of the mice failed to reveal the presence of the *Spirocheta morsus muris.*

Subacute bacterial endocarditis was eliminated because of the persistent negative blood cultures, the absence of cardiac murmurs, and the absence of clinical signs, e.g., substernal pain, café au lait color, embolic phenomena, and enlargement of the spleen. (The spleen became palpable one-half fingerbreadth below the costal margin on June 9, 1935, but could not be palpated again a few days later.)

Roentgenographic studies of the accessory nasal sinuses and mastoid processes were made to rule out the presence of an infectious process in these regions. At no time did the films show any abnormalities.

Typhoid and paratyphoid were eliminated as a possible cause almost immediately because of the high leucocyte count; in addition, a Widal test made on Nov. 23, 1934, was negative.

Undulant fever was considered, but two agglutination tests done on Dec. 17, 1934, and Feb. 15, 1935, were negative.

Still's disease, or chronic polyarthritis, was considered a likely etiologic factor in our case because cutaneous manifestations, such as erythema, erythema multiforme, and urticaria, as well as protracted fever, occur in this disease. Cases of Still's disease have been reported in which the patient had an elevation of temperature for three months or longer before joint involvement occurred.[5] In our case, too, the temperature was elevated for at least three months before the joint manifestations became marked. Against the diagnosis of Still's disease, however, are the absence of symmetrical joint involvement, the absence of wasting and marked limitation of motion, and the absence of enlargement of the liver and superficial lymph nodes. Roentgenologic examination of the elbow, wrist, hip, knee, and ankle joints of our patient on April 20, 1936, failed to show thickening of the periarticular structures, osteo-

porosis, or distention of the joints—changes characteristic of Still's disease. The lower pole of the spleen could be felt one-half fingerbreadth below the costal margin for the first time on June 9, 1935, and for several days after. Later it could not be felt. While it is true that enlargement of the spleen in Still's disease may not be marked, it is Poynton's opinion that it can be felt at least one or two inches below the costal margin in practically every case.[6] Another dissimilarity is the moderate leucocytosis found in Still's disease. Our patient had a marked increase in the number of white cells; indeed, the count reached 41,000 on one occasion. Eosinophilia is observed occasionally in Still's disease; it was absent in our case. Our patient, however, did have a definite increase in the sedimentation rate (Table I). We mention this because Dawson and Boots[7] stressed the increased rate in Still's disease.*

We have mentioned the fact in favor of and against the diagnosis of Still's disease because we feel that it is impossible at this stage of the patient's illness to make a definite diagnosis of Still's disease or to rule it out.

*We have since learned that the case reported by Bilderback in 1930 as a case of fever of unknown etiology of one year's duration is now considered to be definitely one of Still's disease.

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ISOLATED PERIPHERAL RADIAL NERVE PARALYSIS IN THE NEWBORN

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ISOLATED peripheral radial nerve palsy in the newborn has received very little attention in this country. The only reports in the American literature were made by Smith.[1, 2] There are a number of reports in the German literature, and among them two rather comprehensive accounts which contain reviews and comments on all reported cases.[3, 4] We wish to report a case which we believe merits recording, first, because such instances have received little attention in American writings and, second, because other factors than those recognized by writers on this subject may have operated in this infant.

REPORT OF CASE

Maternal and Birth History.—The last menstrual period occurred Sept. 28, 1932, or Oct. 30, 1932. Pregnancy was uneventful except for slight edema of legs and occasionally of face, and with albumin 1+ at times. The measurements were as follows: intercristal 27 cm., intertrochanteric 30 cm., interspinous 23 cm., and Baudelocque 16.5 cm. An unsuccessful attempt at induction of labor with castor oil and an enema was made July 16. The patient was admitted to Mount Sinai Hospital, service of Dr. A. F. Lash, on August 14. At 10 A.M. castor oil, 1½ ounces, was given, followed by quinine sulphate, 5 gr., at 9:45, 10:15, and 10:45 A.M., and an enema at 1 P.M. Irregular pains resulted, which were only slightly influenced by intranasal pituitrin. At 5:35 P.M. pituitrin, minims 3, was given hypodermically and the bag of waters ruptured at 6:50 P.M. At 7:25 nembutal (sodium pentobarbital), 3 gr., was given by mouth and repeated at 7:45 P.M. when dilatation of the cervix was practically complete. Progress was satisfactory until the resistant perineum was encountered, where the head remained one hour with very little advance. At 10:40 P.M. delivery was easily effected by low forceps and episiotomy under ether-nitrous oxide anesthesia. The position of the occiput was left posterior, but rotation anteriorly occurred spontaneously.

Infant History.—The child was a baby girl weighing 6 pounds and 12 ounces (3030 grams) in good condition and with a vigorous cry. The following morning examination revealed a flaccid paralysis of the extensors of the right wrist with resulting wrist drop and slight adduction of the thumb. The circumferences of both forearms and arms were alike. There were no pressure marks or other external or palpable evidences of injury in either the shoulder, arm, forearm, or wrist. Movements at the right shoulder and elbow were normal. The triceps muscle was not involved.

A diagnosis of isolated peripheral radial nerve paralysis was made and the hand placed in a cock-up splint. Massage was done daily. Improvement was rapid, and after ten days the splint was discarded. Recovery was complete in two weeks, and no abnormality was noted after that time. At present, at the age of two years, the child is well and normal in every respect.

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COMMENT

Trauma is considered the essential causative factor in the production of isolated peripheral radial nerve palsy. The radial nerve is most exposed to injury at the lateral surface of the lower one-third of the arm. Compression does occur here at times since hematomas are described at this point in several case reports. Ottow[5] observed a case in which a hematoma was present without radial nerve paralysis. Langen[3] has interpreted these hematoma-like swellings and pressure grooves which occur occasionally in these paralyses of the newborn as due to amniotic bands which are subsequently absorbed. Ottow, however, thinks that the grooves are more likely due to pressure by the umbilical cord and the hematoma-like swellings to compression by the pelvis, since amniotic bands appear very early in gestation and result in more severe deformities and malformations. In our case the absence of involvement of the triceps indicates that the radial nerve was affected below the axilla. The absence of muscular atrophy and the rapid recovery would argue against constriction of the arm by amniotic bands and would indicate pressure recently applied as a more likely etiologic factor. Absence of pressure marks would not necessarily militate against pressure as a possible cause, since none were noted in several reported cases due to compression.[2, 5, 6, 7, 8] In our case arrest of the head at the resistant pelvic floor occurred for about one hour after satisfactory progress. Ottow explains the mechanism of paralysis as due to the compression of the humeri between the promontory and the symphysis at the level of the entrance to the true pelvis, when the head is arrested by the resistant pelvic floor. That compression of both humeri takes place seems likely since Smith's recently reported case and one of Ottow's showed bilateral radial nerve paralysis. Krafft[9] stresses uterine wall pressure and reports a case associated with subcutaneous adiponecrosis reaching to the lateral aspect of the lower third of the forearm (radial point).

Another factor which has hitherto escaped attention and may be of importance is the rôle of maternal medication in the production of this condition. In our case castor oil, pituitrin, quinine, and sodium pentobarbital were administered. The first two may readily be excluded as possible etiologic agents. Quinine and barbiturates, however, may be suspected. No reports could be found in the literature where either of these drugs taken orally by the mother produced peripheral neuritis in the fetus, except perhaps Taylor's case[10] of deafness of the newborn in which the inner ear was involved because of quinine. Nevertheless, cases are recorded in which the intramuscular injections of quinine and urea[11] and barbituric acid derivatives[12] in the upper arm caused radial nerve paralysis. In his explanation, von Uhlenbruck considers a generalized intoxication with localization of the drug in the radial nerve. From this standpoint our case might possibly be included in the group of Saturday night palsies in which pressure on the arm in addition to an intoxication

(alcoholic) causes the paralysis. In only one other of the twenty-nine cases reported, however, was quinine given to the mother. Barbiturates were not given in any of these. In some ten cases of the group, fractures of the humerus were associated with the nerve paralysis.

SUMMARY

1. A case of isolated peripheral radial nerve palsy in the newborn is reported.

2. Compression of the upper arm by the pelvis appears to be the major causative factor in these cases.

3. In our case it is possible that fetal intoxication from a barbiturate and quinine was a contributory causative factor.

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INTESTINAL OBSTRUCTION DUE TO MECONIUM ILEUS IN A NEWBORN INFANT

Case Report

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INTESTINAL obstruction due to stenosis and atresia of various parts of the gut or to constricting bands is not uncommon in newborn infants. From time to time there have appeared in the literature reports of obstruction due apparently to no tumor or congenital malformation of the gastrointestinal tract but to an accumulation of mucilaginous meconium in the tract itself. The term "meconium ileus" has been adopted by most writers to describe this condition. Even in the more complete textbooks of pediatrics there is usually no mention of such a condition. Pfaundler and Schlossman refer to it briefly in their 1935 English edition, quoting a case report from the literature. Finkelstein in his German textbook of diseases of infants says, "Sometimes with the first portion of meconium a gelatinous gray or yellow mucoid mass is passed, 'the meconium plug.' In occasional cases symptoms of intestinal obstruction are caused by mucous plugs rather than malformation; sausage-like, gelatinous or hard masses which consist of mucus, epithelial cells, calcium concretions and sometimes fibrin. They are perhaps related to meconium plugs or may be an evidence of membranous enteritis."

As this form of obstruction is apparently rare, the diagnosis usually difficult and the cause obscure, it seems of interest to report the following case:

Baby C. was born on the outside obstetric service of the Vanderbilt Hospital on Sept. 5, 1934. The child was the result of a full-term normal pregnancy and was born after a normal labor. The mother's blood Wassermann was negative. From birth he refused to take fluids well and vomited what he did take. On the second day after birth it was noticed that he was becoming dehydrated. He was admitted to the hospital the next day, Sept. 7, 1934. He was said to have had one small meconium stool. Nothing abnormal was noted on admission, except marked dehydration. The baby weighed 6 pounds and 10 ounces. The temperature was normal. The hemoglobin was 21 grams; the urine, normal. The Wassermann test was negative. No obstruction was met on rectal examination, but, when the finger was removed from the anus, it was found covered with a thick, dark, gelatinous material which did not resemble ordinary meconium. The child was given subcutaneous saline and placed on a formula of diluted whole milk with sugar. He nursed badly and continued to vomit everything taken. The stools were large grayish green to yellow and resembled

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thick gelatin. The abdomen became markedly distended. A diagnosis of congenital atresia of some part of the intestine was considered, but the passage of such large amounts of material by rectum seemed to make the diagnosis unlikely. As the vomiting and distention increased steadily, it was decided to institute duodenal suction, with attempts at feeding through the duodenal tube later if the vomiting ceased. Meanwhile parenteral fluids were continued. The child's condition improved temporarily, but the vomiting and distention recurred when feeding was started. On the third day after admission the temperature rose sharply; the respirations became rapid; and signs of bronchial pneumonia developed. Ten days after admission the child died.

At postmortem examination the stomach and small intestines were distended and the colon relatively contracted. There was no evidence of volvulus, constricting bands or other external obstruction to the intestine. On examination of the interior of the gastrointestinal tract nothing abnormal was found until the ileum was

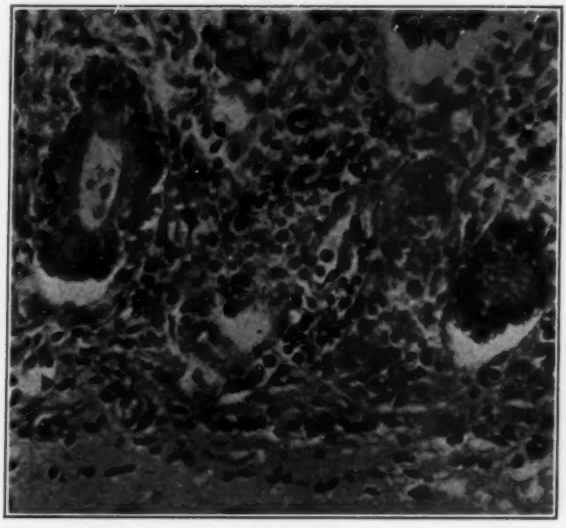

Fig. 1.—Section from ileum showing focus of inflammation in base of mucosa. Note inflammatory cells invading intestinal gland at left. The exudate is composed principally of mononuclear cells; however, a few polymorphonuclear leucocytes are present. (×550.)

reached. Here the intestinal lumen was filled with tenacious, gray mucoid material similar to the material found in the stools during life. When this was removed, the mucosa appeared normal and free from congestion, hemorrhage or ulcers. No obstruction was found in the intestine. The colon was filled with the same tenacious, gray mucoid material. It was described as being of the consistency of stiff jelly and seemed to contain little true fecal matter. The liver appeared normal, and bile was easily expressed from the gallbladder into the duodenum. The spleen was not enlarged. The only abnormality grossly was a small amount of yellow exudate along the notched border. All the organs were normal except the lungs. Here a moderate amount of bronchopneumonia was found. The bones showed no evidence of congenital syphilis.

When microscopic sections of the organs were made, most of the tissues were found to be normal. There was a slight inflammatory reaction of the small intestine

with an increased number of mononuclear cells in the mucosa and even below the muscularis mucosa in the submucosa. A few polymorphonuclear leucocytes were present in the mucosa and submucosa of the duodenum. There was no necrosis or ulceration of the intestine. The muscularis was prominent but not hypertrophied. The serosa was normal. There was partial desquamation of the epithelium of the mucosa. The goblet cells showed no evidence of hypersecretion. A microscopic section of intestine is shown in Fig. 1. A small area of bronchopneumonia was found in the lungs. The liver was normal on microscopic section.

The only organ showing marked changes was the pancreas. Here there was an interstitial pancreatitis characterized by increased fibrosis and a slight degree of inflammation. The fibrosis was marked and was both interlobular and intralobular in distribution. The inflammation was composed principally of mononuclear cells,

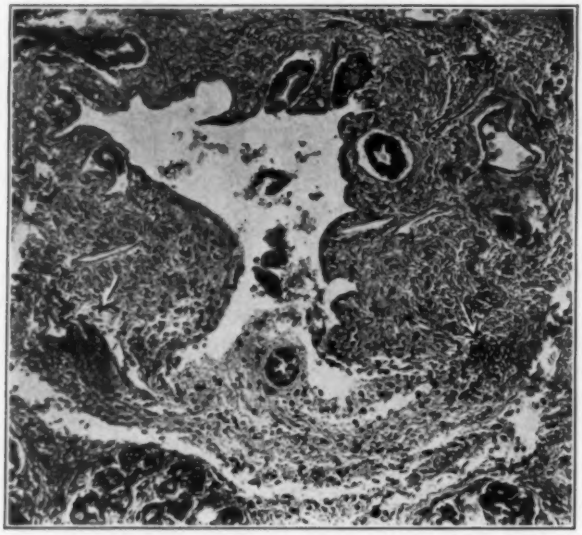

Fig. 2.—Section showing slightly dilated pancreatic duct with desquamation of epithelium and acute inflammation of the wall. Arrows point to fibrinous exudate. (×190.)

lymphocytes, and large mononuclear phagocytes; however, occasional polymorphonuclear leucocytes were present. The inflammation was most prominent in the walls of the ducts and the surrounding fibrinous tissue. There were hemorrhage and fibrin with many polymorphonuclear leucocytes in the wall of two or three of the ducts. A striking feature was the dilatation of the ducts and some of the acini. Many of the ducts and the acini contained a loose pink finely granular precipitate, while some were empty. A few had desquamated epithelium. In no instance was there demonstrable occlusion of the ducts. The islands of Langerhans were normal, and the acini were normal except for dilatation. Microscopic sections of the pancreas are shown in Figs. 2 and 3. From the appearance of the pancreas it seems possible that there may have been a stenosis of the main pancreatic duct. This possibility was not thought of at the time of the postmortem examination, and the sections of the pancreas which were preserved did not permit of settling this point.

In a review of the literature twenty-one reported instances of an apparently similar condition were found. In five cases[1-5] the child after showing symptoms of intestinal obstruction for several days passed one or more large plugs of puttylike meconium and then was well. In the majority of the other cases[6-19] the child had no bowel movements, and the condition was thought to be a congenital developmental obstruction of the gastrointestinal tract. The true cause, obstruction due to thickened intestinal contents, was first revealed either at operation or at postmortem examination. The gastrointestinal tract was always patent, and no external causes of obstruction were found. In most cases the intestine was enormously dilated above the

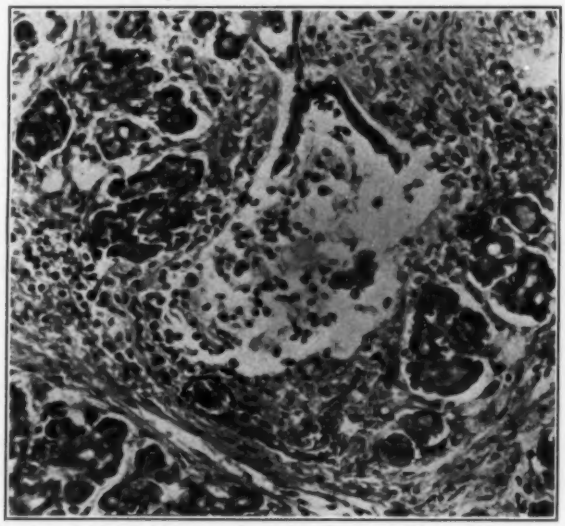

Fig. 3.—Section of dilated pancreatic duct and surrounding acinic tissue. Note the desquamated epithelium and acute inflammation in the duct wall and adjacent tissue.

obstruction, which was usually in the ileum, and was completely collapsed below. In several cases the intestinal musculature was hypertrophied at the point of obstruction. In a few cases there had been rupture of the intestines, and fluid was found in the peritoneum. Many different terms were used to describe the intestinal contents, but the favorite one was that they were of the consistency of thick putty. In the majority of instances only the peritoneal cavity and the gastrointestinal tract were examined, or if other organs were examined only a description of the gross appearance was given. Various theories were then advanced as to the cause of the gummy, puttylike meconium. The favorite theory was that the intestinal con-

tents were thickened because of lack of secretion or too late secretion of bile or pancreatic juice, or perhaps of the glands of the gastrointestinal tract itself.

In five cases in which the other organs were examined, an abnormality of either the liver or the pancreas was found. Kornblitt, Borris, and Otani[7] describe a typical case in a four-day-old child. No meconium had passed from birth. Vomiting and distention appeared on the third day. At operation the child had gas in the peritoneal cavity. There were markedly distended loops of small intestine covered with a pasty brown material. The operation was discontinued because of the poor condition of the child. Death occurred the next day. At postmortem examination a diagnosis of meconium ileus with perforation and generalized meconium peritonitis was made. Microscopic sections of the pancreas showed findings very similar to those reported in the present case. There was a marked increase in the stroma of the pancreas; the acini were atrophic; and in many areas replaced by connective tissue. The main pancreatic duct was extremely widened, and the dilatation of the ducts extended even into the terminal portions involving the acini with the result that the acinic cells were flattened, occasionally resembling small ducts. A small amount of lymphocytic infiltration was the only evidence of reaction about the ducts. Serial sections were made through the head of the pancreas, and the main pancreatic duct was found to be stenotic. It was suggested that the changes in the pancreas corresponded almost exactly to those brought about experimentally after ligation of the pancreatic duct, and that absence of pancreatic juice had caused inspissation of meconium with subsequent intestinal obstruction. Landsteiner[12] describes an almost exactly similar case with operation and death. Here again on postmortem examination marked changes were found in the pancreas. There were an increase in the interlobular and intralobular connective tissue and an infiltration of this tissue with round cells. The ducts were markedly dilated, and the acini and the islands of Langerhans, normal. The pancreatic duct near its lumen was tortuous and folded and without contents. Further on in the pancreas it was wider and filled with exfoliated, mostly unstained, epithelial cells. Landsteiner believes that it was lack of pancreatic secretion that caused the thickening of the meconium. At the end of his article he mentions another case of obstruction due to thickened meconium. The pancreas was normal, but there was no secretion of bile. He says that it looks, therefore, as if both bile and pancreatic juice might be necessary for the formation of meconium of normal consistency. Fanconi[13] also reported a case in which the pancreas was normal. There was bile in the gastrointestinal tract, and yet the liver showed the typical picture of jaundice due to obstruction. The liver cells were bile stained,

and the smallest capillary bile ducts were plugged with bile. There is one more case with a cystic liver described by von Meyenburg,[16] in which the meconium was said to be of a puttylike consistency.

Lesions in the pancreas in infants without symptoms of meconium ileus are not uncommon. In cases in which we have seen interstitial pancreatitis in infants dying from other causes, the lesion was, however, not as severe as it was in our case of meconium ileus. Lack of biliary secretion is also not rare without symptoms of intestinal obstruction. In few of such children seen after the neonatal period is the character of the first stools known.

In the six cases of meconium ileus, including our case, in which complete postmortem examination was done, abnormalities were found in either the liver or the pancreas in every case. It seems probable, therefore, that failure of pancreatic secretion or bile to reach the gastrointestinal tract during fetal and neonatal life is at least part of the cause of meconium ileus.

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A COMPARATIVE STUDY OF AGGLUTININ RESPONSE AFTER PERTUSSIS VACCINATION WITH THE SAUER VACCINE AND WITH A TOXIN VACCINE AND IN UNTREATED CLINICAL PERTUSSIS

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PERTUSSIS vaccination has been the subject of study for many years, but until fairly recently the results reported by various investigators differed so widely that it was hard to judge whether pertussis vaccine was of any value. Recent reports, however, have been rather encouraging. Madsen[1] found in a carefully controlled investigation on the Faroe Islands that there were a definite reduction in incidence and a marked decrease in mortality due to pertussis among the vaccinated children as compared with the unvaccinated controls. Sauer[2] reported very favorable results when he used large doses of pertussis vaccine.

There is at present, however, considerable difference of opinion as to the optimum method of preparing pertussis vaccines and the total dosage that is to be used. The dosage formerly employed was comparatively small, seldom exceeding 10 to 15 billion bacteria. Madsen found that a total of 22 to 30 billion bacteria gave very favorable results. Sauer has tripled this dose. He recommends a dosage of 80 to 90 billion, which is by far the largest ever employed.

The chief points of controversy with regard to the preparation of pertussis vaccines are: (1) whether stock cultures of pertussis are as antigenic as freshly isolated cultures; (2) whether the Bordet-Gengou medium is the only medium suitable for maintaining pertussis cultures and for the preparation of the vaccine; (3) whether human, goat, or sheep blood should be used to enrich the medium.[3]

In considering the above points it is well to bear in mind that the antigenicity of bacteria depends to a large extent upon the conditions under which they are maintained in the laboratory. Some cultures alter rapidly, whereas others retain their original characteristics for a period of years when they are kept under optimum conditions. In preparing typhoid and paratyphoid vaccines, for instance, stock strains of proved antigenicity may be kept for many years, whereas newly isolated strains may be entirely unsuitable.[4] Stock diphtheria bacilli of proved toxigenicity, such as P.W. No. 8, are used for pre-

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paring toxins in preference to newly isolated virulent cultures. Other examples may be given to show that the date of isolation of a culture is by far less important than the condition of the culture at the time that it is used in preparing the vaccine.

With regard to pertussis bacilli, Leslie and Gardner[5] found that the bacilli could be divided into four groups on the basis of their virulence for guinea pigs and the differences in their serologic characteristics; the authors considered these groups as phases of the same type. They found that freshly isolated cultures were virulent for guinea pigs and they placed these in Phase I. Stock cultures that were nonvirulent were placed into Phases III and IV, and a small group of stock bacilli that were slightly virulent, they designated as Phase II. All of the above phases differed serologically. They succeeded in changing pertussis cultures of Phase I to Phases III and IV by special methods of cultivation; thus showing that cultures in Phases III and IV are degeneration stages of Phase I. These changes, however, were slow to appear, and it required special methods of cultivation to induce them. In one instance it took twenty-five months to change Phase I to Phase IV; and that only after the culture was grown on mediums that were not optimal for pertussis bacilli, and by fishing out certain individual colonies. In other instances the change of phase was induced by growing the culture on an Antiphase I Serum and again selecting individual colonies. These artificially induced changes are not comparable to the changes that take place under ordinary conditions in the laboratory. Toomey, Ranta, and Takacs[6] found that pertussis bacilli retain their virulence and antigenicity for a long time when the cultures are maintained on blood medium. Similarly Shibley and Hoelscher[7] found that stock cultures maintain their "S" or virulent form for a period of years when they are maintained on a suitable medium. We found in a study extending over a period of years that pertussis bacilli retain their original morphologic, cultural, and serologic characteristics for a long time (in some instances for a number of years) when the cultures are maintained on an infusion medium that has 25 to 30 per cent of normal blood and that the percentage of blood in the medium determines the loss or retention of its original characteristics. When the amount of blood is decreased below 20 per cent, or when the organisms are grown on blood-free mediums, the growth becomes atypical; the ability to lyze blood is decreased or entirely lost; and the cultures agglutinate poorly in specific serum. On the other hand, cultures that are maintained on Bordet-Gengou medium, or infusion agar plus 25 to 30 per cent of normal animal blood, are characteristically coccoid in form, produce hemolysis on both the above mediums and are agglutinated by specific serums. It therefore appears that pertussis cultures can be maintained

in stock without loss of their original characteristics if they are grown under suitable conditions, and there seems to be no adequate reason for discarding them in favor of newly isolated strains.

The question of the kind of blood that should be incorporated in the medium for growing the cultures should be considered first for its growth-accessory substances and second for the possibility of sensitizing the vaccinated children to the corresponding serum if there should be any need subsequently to use a therapeutic serum.

As far as the growth-accessory substances are concerned, there is no evidence at present that human blood has better growth-promoting substances than animal blood. On the other hand, adult human blood may contain antipertussis antibodies which may cause dissociation and possibly alteration in type, and for that reason it may be undesirable to use human blood.

The possible sensitization to subsequent use of therapeutic serums through the injection of vaccines that are grown on horse's or sheep's blood has probably been the main reason for advocating the use of human blood. In view of the work of Mackenzie,[8] however, there seems to be little danger of sensitizing by the minute amount of serum that may be present in vaccines that are grown on solid blood mediums. Mackenzie found that it was necessary to give a minimum of 100 c.c. of undiluted horse serum to sensitize humans to horse serum and also to some extent to sheep, rabbit, and chicken serums. But the degree of sensitization to the heterologous was very much less than to the homologous serum. In calculating the maximum amount of sheep serum that may be present in pertussis vaccines that are prepared by our method, we find that they contain approximately 0.00041 c.c. of sheep serum per cubic centimeter of vaccine or 0.00328 c.c. of serum in the total dose of 8 c.c. of vaccine, which is the dosage recommended by Sauer. It therefore seems most unlikely that there is any danger of sensitizing to either horse or sheep serum by the minute amount of serum that is present in the vaccine.

Because of the differences of opinion with regard to optimum dosage and methods of preparing the vaccine, we began an investigation about three years ago to determine, if possible, the following points:

1. The comparative antigenicity of vaccines prepared of newly isolated cultures and of stock cultures.

2. The optimum dosage and the optimum intervals between injections for antibody stimulation. The intervals used by different investigators at present vary from two to seven days.

3. A comparative study of agglutinin response after intracutaneous, intramuscular, and subcutaneous vaccination. Tuft, Yagle, and Rogers[9] found in a study of different methods of antityphoid vaccination that small intracutaneous doses of vaccine stimulated agglutinins to the

same or slightly higher degree than much larger subcutaneous doses. We were able to confirm their results with regard to antityphoid vaccinations,[10] and it occurred to us that the intracutaneous method may prove equally satisfactory in pertussis vaccination.

The clinical tests to determine the above points were carried out by Dr. T. E. Waldie, of the New York Foundling Hospital, and it was through his cooperation that we were able to obtain bleedings from the vaccinated children as well as from corresponding unvaccinated controls. We hoped that by studying the agglutinin response after vaccination we may get some information as to the adequacy of the dosage employed, the comparative value of the intramuscular and the intracutaneous methods of injection, and the antigenicity of vaccines that were made of freshly isolated and of stock cultures. Although the presence of agglutinins may not be a direct index of immunity it might help to evaluate the immediate response to vaccination.

We have also studied agglutinin response in clinical pertussis in order to see whether there was any similarity between the time of appearance, the height of the titer attained, and the length of time that agglutinins persist after infection and after vaccination. With these problems in mind we carried through the following experiments:

EXPERIMENT 1: AGGLUTININ RESPONSE AFTER INTRAMUSCULAR AND INTRACUTANEOUS VACCINATION WITH PERTUSSIS TOXIN VACCINE GIVEN AT TWO- AND SEVEN-DAY INTERVALS

This experiment was in the nature of a preliminary test. The vaccine employed in this test was prepared in such a manner that it contained a toxic substance in addition to the pertussis bacilli. We found in a previous investigation[11] that pertussis bacilli are capable of producing a toxic substance and that vaccines containing this toxic substance stimulate agglutinins to a greater degree than those which lack this substance. We therefore prepared our vaccines in such a manner that they contained this toxic substance in addition to the pertussis bacilli. The toxin vaccine was prepared as follows:

Preparation of Pertussis Toxin Vaccines.—Stock cultures were maintained on beef infusion agar, pH 7.2 to 7.4, to which 30 per cent blood was added. Before the vaccine was prepared the cultures were plated on infusion blood agar and on Bordet-Gengou medium, and each culture was examined for characteristic morphology, for hemolysis, and from time to time for agglutination with specific serum. Only those cultures were used in the vaccine that were characteristic morphologically, culturally, and serologically.

Preliminary transplants were made on 1-inch tubes of sheep blood –beef heart agar and incubated for forty-eight hours at 37° C. The

growth from each tube was emulsified in 12 c.c. of 1 per cent sheep serum–beef heart broth of pH 7.2 to 7.4, and 4 c.c. of this broth suspension was inoculated on 30 per cent sheep blood–beef heart agar in Blake bottles. The bottles were incubated for twenty-four hours at 37° C. and were then tilted back and forth to cover the entire surface of the bottle with the liquid inoculum. After an additional twenty-four hours' incubation the growth was washed off with 10 to 15 c.c. of sterile physiologic saline which contained 1 per cent phenol. The vaccine was tested for purity by inoculating blood agar with a sample of the vaccine, and the vaccine was then incubated at 37° C. for twenty-four hours, which is usually sufficient to sterilize it. It was tested for sterility and stored in the ice box at 8 to 10° C. The vaccine was standardized by Wright's method and diluted to contain 10,000 million bacteria per cubic centimeter, also the phenol content was diluted to 0.5 per cent. Each lot of vaccine was tested for the toxic substance, by Shwartzman's method[12] as follows:

A portion of the vaccine was centrifuged to sediment the bacteria, and the supernatant fluid was passed through a W Berkefeld filter. The bacteria-free filtrate was used for the test. Rabbits were given an intracutaneous injection of 0.25 c.c. of the filtrate, and from eighteen to twenty-four hours later they were given an intravenous injection of the filtrate using 1.0 to 1.5 c.c. per kilogram weight of the rabbit. An inflammatory reaction appeared at the point of intracutaneous injection in about four to eight hours after the intravenous injection; this reaction deepened in color until it was dark purple. Some of the rabbits died within one-half hour to three hours after the intravenous injection when the filtrate was very toxic. There was, however, a fairly large percentage of rabbits that were not susceptible to this toxin, and therefore three or four rabbits were used in each test. Either the skin reaction or death was taken as an index of toxicity.

The agglutination studies were carried out as follows:

A group of 190 children was subdivided into eight groups. The children in Group 1 were given intramuscular injections at two-day intervals, and in Group 2 at seven-day intervals. The total dosage in this group was 39 billion bacteria. The third and fourth groups were given a total of 8.5 billion bacteria intracutaneously at two- and seven-day intervals, respectively. Groups 5, 6, 7, and 8 were injected with corresponding amounts of sterile milk instead of vaccine. The milk was diluted to the same opacity as the vaccine, and the injections were given in the same way as the vaccine. So that for each group of children that received the vaccine, there was a corresponding group of controls who received milk.

Bleedings were obtained from the children before the injections and at intervals beginning one week after the last injection was given.

Each case was designated by a number so that the person who read the test did not know whether it was a vaccinated or a control child. The same person made all the readings of the test in order to eliminate individual variations.

The agglutination antigen used in these tests was a suspension of the bacteria in physiologic saline containing 0.1 per cent formalin. This suspension was diluted to the desired concentration and standardized with a known pertussis serum. A control of the antigen with this serum was used in every test in order to control the sensitivity of the antigen. Every new antigen that was prepared was standardized in this manner.

The serums were diluted with saline beginning with a 1:5 dilution and doubling each succeeding dilution. Then equal amounts of serum dilution and antigen were mixed in small tubes and incubated at 55° C. overnight. The titer of the serum was determined by taking the highest dilution of the serum that showed definite clumps.

With very few exceptions the normal preinjection bleedings were either negative or agglutinated in a low titer, usually below a 1:20 dilution of the serum. In two instances the normal bleedings showed a titer of 1:60 and 1:80, respectively, but on investigation it was found that one of these children was recently transferred from the Misericordia Hospital and that he had just recovered from pertussis and that the other was intimately exposed to pertussis and may have had an abortive attack. Both of these children were excluded when the results were charted.

In charting our results we considered agglutination not above 1:20 as within the normal range and 1:20 or above as positive. The results of the first experiment are given in Table I.

TABLE I

AGGLUTININ RESPONSE AFTER INTRAMUSCULAR INJECTIONS OF PERTUSSIS TOXIN VACCINE AND OF STERILE MILK

VACCINE	METHOD OF INJECTION	INTERVAL BETWEEN INJECTIONS	TOTAL PERTUSSIS BACTERIA	NUMBER OF CASES	AGGLUTININ INCREASE*	PER CENT POSITIVE
Toxin vaccine, 10 billion per c.c.	Intramuscular	2 days	39.0 bil.	23	8 cases	34.7
		7 days	39.0 bil.	19	2 cases	10.5
	Intracutaneous	2 days	8.5 bil.	25	9 cases	36.0
		7 days	8.5 bil.	25	2 cases	8.0
Control, sterile milk	Intramuscular	2 days	0	28	5 cases	17.8
		7 days	0	24	5 cases	20.8
	Intracutaneous	2 days	0	20	0 cases	0
		7 days	0	26	2 cases	7.6

*Agglutination titer varied between 1:20 and 1:960—average 1:70.
Total vaccinated, 92.
Total controls, 98.

The agglutination response in this test was rather low. Most of the children showed no increase in agglutinins above the normal range. But of those that did show some increase, the response was better in the two-day than in the seven-day interval group and was somewhat better in the intracutaneously vaccinated group than in the intramuscular, although the total dosage given intracutaneously was one-fourth of the intramuscular dose.

The results in the control group were somewhat disconcerting. As shown in Table I there was an increase of agglutinins in some of the children who were injected with milk instead of vaccine—17 per cent and 20 per cent, respectively, in the two- and the seven-day intramuscularly injected children, and 7 per cent in the seven-day interval intracutaneously injected children. None of the children in the two-day interval intracutaneously injected group showed any increase in agglutinins. It seems difficult to explain why milk should stimulate agglutinins for pertussis, except on the basis of nonspecific stimulation of latent agglutinins due to a possible previous infection, as some of these children must have had ample opportunity of exposure before they were brought to the hospital.

From the results obtained in this test, it would seem that intracutaneous injections at short intervals might be the method of choice. However, since the groups studied in this experiment were rather small, no definite conclusions can be drawn at this time until further comparative tests are made.

EXPERIMENT 2: AGGLUTININ RESPONSE AFTER VACCINATION WITH LARGE DOSES OF PERTUSSIS VACCINES MADE OF NEWLY ISOLATED AND OF STOCK CULTURES

This experiment was planned to determine whether large doses of vaccine would give a corresponding increase in agglutinins, also to compare the antigenicity of vaccines made of stock cultures that have retained their original morphologic, cultural, and serologic characteristics and of freshly isolated cultures. A group of 60 children was used in this test. These children were divided into two groups. One group of 30 children was given a vaccine prepared according to Sauer's method, i.e., newly isolated cultures grown on human blood–Bordet-Gengou medium*; and a similar group was given our toxin vaccine which was made of stock cultures that have retained their original characteristics. The cultures used in our vaccine were grown on sheep blood infusion agar, and the vaccine contained a toxic substance in addition to the bacteria. The concentration of bacteria was the same in both vaccines—10 billion bacteria per cubic centimeter. The injections were made intramuscularly at seven-day intervals giving 1, 1.5,

*This vaccine was obtained through the courtesy of Dr. Sauer from Eli Lilly & Co.

and 1.5 c.c. into each arm, a total of 80 billion bacteria. This method was chosen in order to make the test comparable with the method employed by Sauer.

Bleedings were taken from the children before the vaccines were injected and again one, two, three, and four weeks after the last injection of the vaccine. These bleedings were tested in the same manner as in the first experiment. Due to various unforeseen conditions, the immunization was not completed in eight children of the Sauer vaccine group, and in 5 of our vaccine group; they were therefore excluded when the results were charted. This left a group of 22 chil-

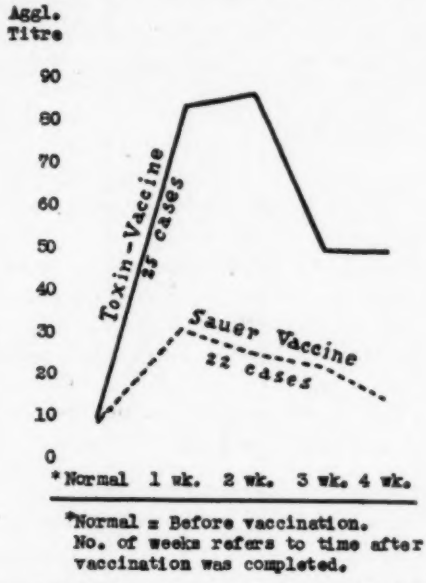

Chart I.—Average agglutinin titers of children injected prophylactically with 80 billion bacteria of the Sauer and of the toxin vaccine.

dren who received 80 billion bacteria of the Sauer vaccine and 25 children who received a similar dose of our toxin vaccine.

The agglutinin response in both these groups was very much better than in those who received a much smaller dosage as shown in Experiment 1 although there were still a considerable number of children among them who showed no increase in agglutinins.

In the Sauer vaccine group of 22 children, 12, or 55 per cent, showed an increase of agglutinins, and 10 remained within the normal range. In the group of 25 children who received our toxin vaccine, 21, or 84 per cent, showed an increase, and 4 remained in the normal range.

There was considerable variation in the individual agglutinin titers in both groups. In charting the results we used the average response

of the group as a whole, including those that showed no increase in agglutinins. The results are given in Chart I.

As shown in this chart, the average agglutinin response of the toxin vaccine group was very much higher than that of the Sauer vaccine group. This may have been due to the additional stimulation of the toxic substance in the vaccine and confirms our previous findings in rabbits.[11]

The maximum titer in both groups was attained between one and two weeks after the last injection of the vaccine, and then it dropped rapidly although it was still above normal at the end of four weeks. We did not make any examinations later than four weeks and, therefore, do not know how long they remained above normal. This corresponds with the results obtained by Kristensen and Ahrend Larsen[13] in complement fixation studies of vaccinated children. They found that the highest complement fixation titers were obtained in the first two weeks and that they decreased rapidly after that.

From the results obtained in this experiment two things stand out clearly: (1) That the agglutinin response to vaccination was largely proportional to the dosage employed. In cases in which the dose did not exceed 8.5 billions given intracutaneously or 39 billions given intramuscularly (Experiment 1) only a small percentage of the children showed an increase in agglutinins. When the dose was 80 billion bacteria, 55 to 84 per cent of the children had an increase of agglutinins. (2) That a vaccine prepared of stock cultures compared very favorably with the one prepared of newly isolated cultures in that it stimulated agglutinins to a higher degree.

EXPERIMENT 3: A STUDY OF AGGLUTININS IN UNTREATED PERTUSSIS CASES AND IN NONPERTUSSIS RESPIRATORY INFECTIONS

Our next problem was to study agglutinins in pertussis cases in order to determine whether there is any similarity between the time of appearance, the height of the titer attained, and the length of time that agglutinins persist after infection and after vaccination. Through the courtesy of Dr. I. Herbert Scheffer, of the Willard Parker Hospital, we were able to obtain sequent bleedings from 65 definite and suspected pertussis cases, and also from 12 patients with nonpertussis respiratory infections. The bleedings were taken as soon as the patients were admitted to the hospital, and in most cases weekly bleedings were obtained until early convalescence. The bleedings were tested for agglutinins in the same manner and with the same antigens as in the previous experiments.

There was a marked variation in the agglutinin titers of the individual pertussis cases which apparently did not correspond to the severity of the infection. In 9 cases there was no increase above the

normal range; in 8 cases it was approximately the same as in the vaccinated; and in 40 cases it was high. In every case in which there was an increase in agglutinins, they increased rather rapidly until the maximum was reached and after that there was a more or less rapid decrease.

Chart II shows the highest and lowest titers that were obtained in individual cases of clinical pertussis, and these are compared with those of the children who were vaccinated with the Sauer vaccine, and with

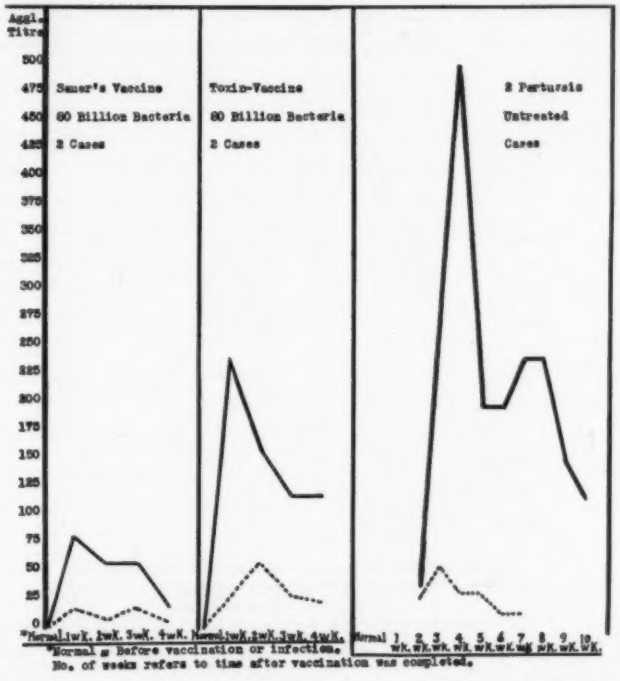
Sauer's Vaccine
60 Billion Bacteria
2 Cases
Toxin-Vaccine
60 Billion Bacteria
2 Cases
2 Pertussis
Untreated
Cases
Normal 1wk. 2wk. 3wk. 4wk.
Normal 1wk. 2wk. 3wk. 4wk.
Normal 1 wk. 2 wk. 3 wk. 4 wk. 5 wk. 6 wk. 7 wk. 8 wk. 9 wk. 10 wk.
*Normal = Before vaccination or infection.
No. of weeks refers to time after vaccination was completed.

Chart II.—The highest and lowest agglutinin responses that were obtained in the groups of children who were injected with the Sauer vaccine and with toxin vaccine and in the untreated cases of pertussis.

the toxin vaccine. In none of the vaccinated children did the agglutinin titer attain the height of the infected children. Among the vaccinated children, however, the highest titer was obtained in the group that received the toxin vaccine.

In Chart III are summarized the results obtained in Experiments 2 and 3. The average agglutinin response in the group of 65 pertussis cases is compared with those of the normal children who were vaccinated with the Sauer and the toxin vaccines. The initial time given in the graph of the pertussis cases is only approximate, as we had to

rely on the histories in each case, and they were dated from the time symptoms were first noted.

The average agglutinin titer in the pertussis cases differs markedly from that of the vaccinated children in the length of time at which the maximum was obtained and in the height of its curve, but it resembles it, in that having reached the maximum, it dropped very rapidly. Dr. Scheffer[14] observed that in most of the pertussis cases in this group there was a marked clinical improvement at about the time that the maximum agglutination titer was obtained. It appears therefore that agglutinins decreased almost as soon as active infection stopped and convalescence began. This corresponds closely to the decrease in

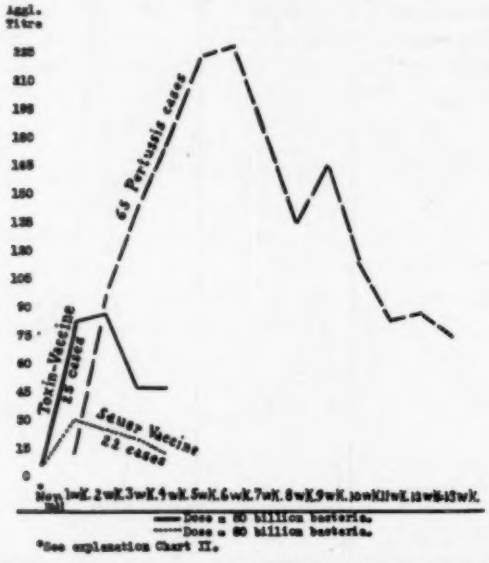

Chart III.—Average agglutinin titers of children injected prophylactically with Sauer's vaccine and with toxin vaccine and of untreated cases of pertussis during the infection and early convalescence.

agglutinins in the vaccinated children soon after the stimulation by the vaccine is discontinued.

The results obtained in the agglutinin studies of the 12 cases of non-pertussis respiratory infection were as follows:

Ten children had normal titers, i.e., negative or not over 1:20 dilution; 1 child had a titer of 1:60, and another of 1:200. These last two children, however, had a history of definite exposure and may have had a mild infection which would account for the high agglutinin titers.

SUMMARY

Agglutination studies were made on several different groups of children who were given injections of pertussis vaccines, in untreated

clinical pertussis and in nonpertussis respiratory infections. The object of these studies was to determine the following points:

1. The optimum dosage for vaccination.

2. The comparative antigenicity of vaccines that are made of freshly isolated and of stock pertussis bacilli.

3. The comparative value of the intramuscular and the intracutaneous methods of administering the vaccine when given after short or long intervals.

4. The agglutinin response after vaccination and during infection and early convalescence. The results obtained were as follows:

a. The average agglutinin response in the vaccinated children was, on the whole, proportional to the dosage given. In those in whom the maximum dose did not exceed 8.5 billion bacteria given intracutaneously or 39 billion bacteria given intramuscularly, only a few of the children showed an increase in agglutinins; although the titer of some of those that did show an increase was fairly high. On the other hand, a dose of 80 billion bacteria stimulated agglutinins in a large percentage of the children (55 per cent in the group that received Sauer's vaccine and 84 per cent in the group that received our toxin vaccine).

b. The intracutaneous method compared favorably with the intramuscular method in stimulating agglutinins although the dose used intracutaneously was very much smaller than the intramuscular dose.

c. The agglutinin response was better in the groups that were given the injections at two-day than at seven-day intervals. However, the groups studied were very small, and therefore definite conclusions cannot be drawn at present.

d. The agglutinin response was better in the group of children who were injected with a vaccine that was made of stock cultures that were grown on sheep blood infusion agar (toxin vaccine) than in those who were injected with a vaccine that was made of freshly isolated cultures that were grown on human blood–Bordet-Gengou medium (Sauer).

e. The agglutinin response in pertussis cases differed markedly from that of the vaccinated children, in the length of time at which the maximum was attained and in the height of its curve (Chart 3). But having attained the maximum (the maximum titer differed widely in different cases) it dropped rapidly. It corresponded closely in this respect with the drop in the agglutinin titer of the vaccinated children. It seems therefore that there was a decrease in agglutinins almost as soon as infection ceased and convalescence began. This again corresponds with the decrease in agglutinins in the vaccinated children soon after the active stimulation of the vaccine was discontinued.

f. The agglutinin content of the serums of all but 2 of 12 children who had nonpertussis respiratory infections was in the normal range. These 2 children were definitely exposed to pertussis and may have had a mild infection which would account for their high agglutinin titers.

CONCLUSION

1. As far as it can be judged from the agglutinin studies, a dosage of 50 to 80 billion bacteria seems indicated in pertussis vaccination when given intramuscularly or subcutaneously.

2. The intracutaneous method of administering the vaccine has given very promising results and may prove to be the method of choice if further tests will confirm our present findings.

3. Potent vaccines may be prepared of stock cultures provided they retain their original morphologic, cultural, and serologic characteristics. The potency of the vaccine may be increased by preparing the vaccine in such a manner that it contains a toxic substance in addition to the bacteria. Sheep blood infusion agar of pH 7.2 to 7.4 was found suitable for preparing pertussis vaccines.

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RHEUMATIC HEART DISEASE IN CHILDHOOD

A Clinical and Postmortem Study of Seventy-Three Cases

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THE outlook for the rheumatic child both as to morbidity and mortality has been studied in the mass in many cardiac clinics. The average wastage over periods of years has been computed in large groups of cases. Less attention has been given to the factors which influence the prognosis in the individual case. What determines an early fatal issue? Does the manner of onset, whether with chorea, polyarthritis, or carditis play a significant rôle? Is the child overwhelmed by a single virulent rheumatic attack, or does he succumb to repeated bouts of infection? To what extent do rheumatic nodules, or pericarditis, or multivalvular involvement influence the prognosis? Is the age of the child at the onset of the rheumatic infection of importance in determining the outlook?

In the effort to gain information on these and other points concerning the life history of the rheumatic infection, we have made a critical study of the clinical and postmortem findings in seventy-three cases of rheumatic heart disease observed at the Children's Memorial Hospital. Inasmuch as the hospital does not retain patients who have attained the age of thirteen years, the present material includes only those patients whose illness terminated below this age limit.

Because of the fact that the work has been chiefly statistical in nature, we shall first set out our findings in tabular form, followed by a discussion of those features which seem to us to be worthy of comment.

Total number of cases, 73
Males—30
Females—43

A. History		
1. Incidence of predisposing causes		
a. Sore throats		
Frequent		18
Infrequent		21
b. Tonsils		
In		55
Out		18
Before first rheumatic attack		11
After first rheumatic attack		4
Questionable		3
c. Growing pains		5
d. Scarlet fever		4
e. Family history		
Rheumatism in other member of family		13

From the Cardiac Service of the Children's Memorial Hospital, Chicago. Dr. Joseph Brennemann, Physician-in-Chief.

2. Incidence of rheumatic phenomena		
a. Chorea		
One attack		15
Two attacks		4
b. Joint pains		
One attack		33
Two attacks		10
Three attacks		3
Many attacks		4
c. Carditis		
One attack		29
Two attacks		22
Three attacks		8
Four attacks		6
Five attacks or more		4
Questionable		3
B. Physical Examination		
1. Valvular involvement		
Mitral		49
Mitral and aortic		19
Functional murmur		2
No murmur		3
2. Pericardial friction		35
Complaint of pain	26	
Absence of pain	9	
3. Arrhythmia		
Fibrillation		7
4. Nodules		
Present		27
C. Postmortem Examination		
1. Valvular involvement		
Mitral		16
Mitral and tricuspid		9
Mitral and aortic		14
Mitral, aortic, and pulmonary		1
Mitral, tricuspid and pulmonary		1
All valves		6
No valvular involvement		1
2. Pericarditis		62
3. Amount of pericardial fluid in cases of pericarditis		
No fluid		39
Less than 100 c.c. (5 to 75 c.c.)		16
100 c.c.		3
125 c.c.		2
150 c.c.		1
200 c.c.		1
Over 200 c.c.		0
4. Cause of death		
Rheumatic heart disease		67
Bacterial endocarditis		2
Staphylococcic septicemia		2
Renal insufficiency		1
Pneumonia		1
D. Observations Relative to Duration of Rheumatic Infection (First rheumatic manifestation to death)		
1. Average age at onset		6.3 yr.
Average duration		1.4 yr.

2. Age at onset	No. of cases	Average duration
3 yr.	5	0.4 yr.
4 yr.	12	1.5 yr.
5 yr.	14	1.5 yr.
6 yr.	9	1.5 yr.
7 yr.	9	1.1 yr.
8 yr.	6	1.8 yr.
9 yr.	9	1.7 yr.
10 yr.	7	1.1 yr.
12 yr.	1	0.5 yr.
Questionable	1	

3. Mode of onset

	Average duration
Of 6 cases beginning with chorea	1.7 yr.
1 died within 3 months of onset	
2 died within 2 years of onset	
6 died within 3 years of onset	
Of 41 cases beginning with joint pains	1.5 yr.
11 died within 3 months of onset	
16 died within 6 months of onset	
20 died within 1 year of onset	
30 died within 2 years of onset	
34 died within 3 years of onset	
37 died within 4 years of onset	
41 died within 5 years of onset	
Of 25 cases beginning with carditis	1.1 yr.
8 died within 3 months of onset	
14 died within 6 months of onset	
16 died within 1 year of onset	
20 died within 2 years of onset	
22 died within 3 years of onset	
24 died within 4 years of onset	
25 died within 5 years of onset	

4. Combinations of rheumatic manifestations

Chorea, joint pains, and nodules	5 cases	2.5 yr.
Chorea	5 cases	1.8 yr.
Joint pains and nodules	19 cases	1.7 yr.
Chorea and joint pains	9 cases	1.4 yr.
Joint pains	17 cases	1.1 yr.
Carditis alone	15 cases	0.8 yr.
Nodules	3 cases	0.4 yr.
Chorea and nodules	0 cases	

DISCUSSION

An analysis of our figures relative to what are usually regarded as predisposing causes of rheumatism shows that these predisposing causes were absent in a large percentage of the cases. That the rheumatic infection occurs more frequently in regions where respiratory infections are prevalent is a well-recognized fact. A cold or sore throat often occurs a few days or weeks before the onset of definitely rheumatic phenomena. These observations have naturally raised the question of the etiologic significance of upper respiratory infections in the rheumatic process. In our group of cases, only one-fourth gave a history of frequent sore throats; about one-fourth were subject to infrequent attacks; and almost one-half gave a negative history. It is doubtful

whether these figures differ significantly from those which would obtain from a group living under similar conditions without any rheumatic manifestations.

Not only has the occurrence of sore throats been emphasized as a probable etiologic factor in the rheumatic infection, but chronic tonsillar infection has also been considered an important predisposing cause. Indeed the tonsil has been viewed with so great suspicion that in many clinics the appearance of any rheumatic manifestation is considered an indication for tonsillectomy as soon as the patient's condition will permit, and this regardless of evidence of tonsillar infection. In this connection it is of interest that eleven children, or 15 per cent of the group, had been subjected to tonsillectomy prior to the first rheumatic attack.

"Growing pains" were encountered in only five of the histories. The fact that this complaint was so rarely obtained in this group of cases would seem to indicate that the indefinite aches which the laity usually interpret as growing pains are of minor importance in the rheumatic infection.

In only four instances was there a history of scarlet fever. In all four of these cases joint pains occurred within a few weeks or months following the scarlet fever. This would suggest that the scarlet fever acted as a predisposing cause, just as other respiratory infections seem to do in an appreciable percentage of cases.

When we come to a consideration of the admittedly rheumatic phenomena, we find that chorea was present in one-fourth of the patients. This figure is surprisingly high in view of the fact that chorea is considered the rheumatic manifestation least likely to be accompanied by cardiac involvement and that, when carditis does occur, it is usually of milder type than when the invasion of the heart is ushered in by an acute polyarthritis.

The involvement of the joints is the "most rheumatic" of all the rheumatic phenomena, being the most frequent mode of onset, and the symptom-complex which calls attention to the danger which threatens the heart. Yet in almost one-third of the cases, there was a complete absence of joint pains. Of those who gave a history of joint pains, the majority had but a single attack, and only 10 per cent had more than two attacks.

One of the most interesting findings concerned the number of attacks of carditis. In 40 per cent the first attack proved fatal. This is so strikingly at variance with the usual teaching that it is deserving of emphasis. Sir Thomas Lewis,[1] in writing on rheumatic carditis, says, "Death may occur in acute and very severe cases, but these are rare. A first attack is rarely fatal." White,[2] discussing the course and prognosis of rheumatic heart disease, says, "It is usual for the child to survive the first rheumatic infection whether it is frank rheumatic fever, chorea, ill-defined sickness, or rheumatic heart infection alone." Other author-

ities make similar statements. We are frank to confess that we had held the same view, even though we had observed the course of the majority of the children whose case histories comprise this report. Only when we were confronted by the statistics did we appreciate how large a percentage of the children succumbed to the initial bout of carditis. Perhaps our own erroneous impression, and that of others, may be explained by the fact that the patient with chronic heart disease who has been followed in the out-patient department, and who has been repeatedly in the hospital, is naturally more familiar to the clinician and is better remembered than the patient who has not been in attendance at the out-patient clinic, and whose first hospital stay closes the picture.

Turning to a discussion of the physical findings, we find pericardial friction was heard at some time during the course of the illness in practically half of the cases. This is a significantly high percentage when one considers that the early stages of the infection were rarely followed in the hospital, that a transient friction rub might easily escape notice, and that pericarditis might occur in the absence of a friction rub. The importance of precordial or upper abdominal pain in pointing to pericardial involvement is revealed by the fact that pain was complained of in twenty-six of the thirty-five cases in which pericardial friction was heard.

Auricular fibrillation occurred in seven instances. Once established it persisted until death in all except one. In this case fibrillation continued over a three-week period seven months before the fatal termination and recurred during the last week of life. Our findings were in accord with other observations to the effect that auricular fibrillation is an ominous sign in the rheumatic heart disease of children and may usually be looked upon as a terminal event. Of the seven children who exhibited fibrillation, two were nine years old, and the remaining five were ten years old when the fibrillation began.

Rheumatic nodules were found in twenty-seven of the seventy-three cases. Here again the figures doubtless fail to give the full incidence of this important rheumatic manifestation. We do believe, however, that they represent very nearly the percentage occurring during the period of hospitalization. Not only were the children inspected repeatedly by members of the attending staff, but our nurse in charge was very zealous in her search for nodules and was deeply chagrined if she failed to be the first to detect them. All writers on rheumatism emphasize the importance of the rheumatic nodule as indicating a heavy degree of saturation with the rheumatic virus and a consequent bad prognosis. The significance of their absence has not been so fully considered. Indeed the failure to discover rheumatic nodules in over 60 per cent of the cases implies that their absence is by no means a necessarily good omen. In fact, it was in the children whose courses ran rapidly downhill that nodules were least often found. In other words, rheumatic

nodules are seldom found in children who are lightly infected by rheumatism and are often absent in those who are overwhelmed by it. Nodules appear in the children who are seriously infected, but who show some degree of resistance to its ravages.

The postmortem studies revealed the presence of mitral involvement in every case except one. This verified the usual teaching that the mitral valve is practically always invaded in the rheumatic heart disease of childhood. The aortic valve was involved in 46 cases, the tricuspid in 41, and the pulmonary in 8. The most frequent combination of valvular involvement was mitral, aortic, and tricuspid, occurring in 25 instances.

Only eleven patients in the series failed to show the presence of pericarditis. Four of these eleven died a noncardiac death. The high incidence of pericarditis found postmortem emphasizes its importance in the severe carditis of childhood. It also emphasizes the fact that even though the presence of pericarditis cannot be proved by the detection of a friction rub, one has a right to suspect pericardial invasion in the child who shows the signs of serious rheumatic heart disease.

One of the perplexing problems presented by the child with rheumatic heart disease who reveals on physical and roentgenographic examinations a markedly increased cardiac outline is whether the enlargement is due to cardiac hypertrophy and dilatation or to pericardial effusion. We feel that the postmortem observations offer convincing evidence on this point. In no case was there more than 200 c.c. of fluid in the pericardial sac. Only one contained this amount, and six others contained between 100 and 200 c.c. of fluid. Certainly amounts so small would in no way embarrass the heart, nor would they be easy of detection either by physical or roentgenographic examination. White[2] says, in speaking of pericardial effusion, "An amount less than 150 c.c. is probably not discoverable by any method of examination since it produces no definite signs."

Numerous writers have emphasized the rarity of massive effusion in rheumatic heart disease. Carey Coombs[3] said, "The diagnosis of pericardial effusion in rheumatic heart disease is still a field for much erroneous thinking, in spite of the work of Lees, Poynton, and others, who have shown by correlation of clinical with postmortem data that effusion rarely attains a bulk sufficient to cause physical signs and that the signs commonly supposed to be due to effusion are in reality caused by acute dilatation of the heart. Skiagraphy is rarely practicable, the patient being too ill to be moved; and it is only in the presence of large effusions, such as do not occur in cardiac rheumatism, that skiagraphy is of any value. Exploratory puncture should be resorted to with the utmost caution: no case in which subsequent events have shown that it would have been justifiable has come under my notice." Yet this view has not gone unchallenged. Sutton[4] has advocated paracentesis of the pericardium as a therapeutic measure in rheumatic pericarditis. Using the

posterior site, she did pericardial taps on eleven children, removing varying amounts of fluid up to 400 c.c. In most instances 200 to 300 c.c. of fluid were obtained. Sutton admits that it is doubtful whether the ultimate result in rheumatic pericarditis is altered, but she is convinced that the symptoms of marked dyspnea, orthopnea, cyanosis, and a sense of pressure and suffocation may be ameliorated by the removal of part or all of the pericardial fluid. We are unable to explain the large amounts of fluid in the cases reported by Sutton compared with the absence or minimal amounts of fluid which were obtained in our cases unless it be a difference in climate and environment influencing the behavior of the rheumatic infection. Certainly there was no indication for paracentesis of the pericardium in the group here reported, either to increase the patient's comfort or as a lifesaving procedure.

The mode of onset of the rheumatic infection has been considered an important factor in determining the prognosis. Findlay[5] says, "Of 80 cases of cardiac disease following chorea, 22.5 per cent ended fatally; whereas of 313 examples following arthritis, 27.7 per cent ended fatally during the same period of time. The prognosis is, however, most serious when carditis is the first or only manifestation of the disease. The mortality incidence in the examples which commenced with carditis, but which were afterwards followed by rheumatism (chorea, arthritis, or nodules) was 42.8 per cent, and in those in which carditis was the sole manifestation of the disease, 66.6 per cent." In the estimation of the seriousness of the prognosis by the duration of the infection in fatal cases rather than the percentage mortality in a given period of time, our figures are in complete agreement with those of Findlay. Of six cases beginning with chorea, the average duration was 1.7 years. In the forty-one instances in which arthritis was the first manifestation, the average duration was 1.5 years. When the carditis itself was the first manifestation, the period of survival averaged only 1.1 years; and when carditis was the sole rheumatic episode, the average time from onset to death was only 0.8 year.

The above statistics do not convey an adequate notion of the behavior of the rheumatic infection in this group. A closer scrutiny of the figures reveals the fact that whereas a relatively small percentage survived for several years, a surprisingly large number survived for only a few months. Twenty children died within three months of the first rheumatic manifestation, and within the succeeding three months eleven others had succumbed. The second half year accounted for the death of six others. Thus it is seen that 27 per cent had died within three months, 42 per cent had died within six months, and 50 per cent had died within one year of the onset. We have already called attention to the fact that the initial bout of carditis resulted fatally in 40 per cent of the cases. The figures just quoted show that the course of the fatal attack was relatively rapid. Any disease which claims an appreciable percentage

of its victims within three months of onset can scarcely be said to be an essentially chronic disease. While numerous writers have called attention to the occasional fulminant case of rheumatic carditis, we do not believe that the frequence of this type has been sufficiently appreciated. Yet we are convinced that our findings are not exceptional, if comparison be made where climatic conditions are similar to those obtaining in Chicago. In a study of the development of mitral stenosis in young people, Bland, White, and Jones[6] reported the duration of rheumatic infection in one hundred patients living in the vicinity of Boston who died at or before the age of twenty-one years. Of their group, twenty died within six months of the onset. This percentage, while lower than in our series, is high, especially when it is recalled that their material included individuals through the age of twenty-one years while our own series was comprised wholly of children under thirteen years of age.

SUMMARY

A clinical and postmortem study of seventy-three children with rheumatic heart disease has revealed the following:

1. Predisposing causes of the rheumatic infection, such as sore throats, chronic tonsillar infection, growing pains, and scarlet fever, were encountered with less frequence than was anticipated.
2. Chorea occurred in 26 per cent and joint pains in 68 per cent.
3. The first bout of carditis proved fatal in 40 per cent.
4. Pericardial friction was heard in 48 per cent.
5. Pericarditis was found on postmortem examination in 85 per cent. In no instance was a large amount of fluid present in the pericardial sac.
6. Auricular fibrillation was infrequent, occurred in the older patients, and was usually a terminal event.
7. Nodules were found in 37 per cent.
8. Average duration of life was longest when the attack began with chorea, less prolonged when joint pains initiated the infection, and shortest when the invasion of the heart itself was the only evidence of rheumatism.
9. The total duration of the rheumatic infection was less than three months in 27 per cent.

We are indebted to Dr. William G. Hibbs, attending pathologist, for the privilege of reviewing the postmortem records.

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Critical Review

SURGICAL PEDIATRICS

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TO THOSE who for many years have been keenly cognizant of the definite and distinct differences between the surgery of adults and that of infants and children, it is most gratifying to note the recent trend toward a more general recognition of these differences and of the fundamental conditions upon which they depend. Among the several excellent articles in the medical literature of the past year those by Penberthy,[1] Burton,[2] and Brunkow[3] are particularly worthy of mention. They point out clearly the differences in structure, proportions, reactions, growth factors, psychology, physiologic requirements and pathologic processes between the rapidly growing infant or child and the adult. The child is an organism in a relatively unstable state of rapid evolution while the adult is in a comparatively stable condition with a gradual progression toward the major involution so well described by Warthin.[4] These differences have resulted in the development of the specialty of pediatrics which requires a constant appreciation and evaluation of these various factors and has given rise to such terms as the "pediatric attitude" or the "pediatric approach." The knowledge of these fundamental differences forms a subconscious screen or filter through which one dealing with children must pass all observations if he is to see conditions in true perspective and arrive at correct conclusions.

Broad experience and keen surgical judgment are evident in the articles mentioned, attention being directed particularly to conditions peculiar to infancy and childhood, the necessity of conservation of body heat, adequate fluid and food supply, skill and delicacy in handling tissues, hemostasis, anesthesia, and especially to the necessity and value of close cooperation between the surgeon and pediatrician. The last point is particularly to be heeded by the occasional surgeon who considers it an unwarranted invasion of his domain for the pediatrician to make suggestions or recommendations regarding the condition of the patient or the choice of time for operation.

Until the rather exclusive specialty of surgical pediatrics develops further, there should be in every community some surgeon particularly adept at handling children[5] who will devote his attention to a study of the essential differences between children and adults and develop ability in this branch of surgery. The differences are not only physical but mental, and he should take into account the effect of illness, therapeutic procedures and hospitalization upon the emotional development of the child,[6] recognizing that many of the psychologic maladjustments of adult life have their origin in childhood, and being particularly careful to minimize the psychic shock which is too frequently associated with illness and the child's contact with the medical profession.

ANESTHESIA

With the great variety of anesthetic agents at present available, individualization of anesthesia is particularly important and relatively easy to accomplish.[7] It seems superfluous to say that the anesthetist should know the condition of the child, but too frequently there is a lack of cooperation between the surgeon and the anesthetist with the result that the anesthetist has little time to determine the type of anesthetic best suited to the patient and no time to gain the child's confidence. Conservation of the surgeon's time is given preference over the present physical and future psychic condition of the patient. This situation is no doubt due to the safety and widespread use of ether, which is so well suited to the average case that its disadvantages as compared to the newer anesthetic agents are overlooked. Especially to be mentioned in this connection are avertin, the barbiturates, cyclopropane, and the use of preanesthetic medication. The statement that these agents are contraindicated in the extremes of life should be revised. Such a generalization is unwarranted as regards children and would appear to indicate unfamiliarity with this age group rather than the result of careful observation and study. Due care and judgment must be exercised in the administration of anesthetics as well as of any other potent drug regardless of the age of the patient, and unwillingness to study the requirements of infants and children and to make the necessary adjustments in suitable cases is a type of mental inertia which should not be tolerated as an excuse for the use of inferior methods.

Cyclopropane is steadily gaining in favor. It is emphasized, however, that it must be used by a skilled anesthetist[8] and requires special apparatus. In one series of 1,108 cases the youngest patient was ten days of age,[9] and in older children, when combined with avertin as a basal anesthetic, it has proved to be as near the ideal as any anesthetic yet employed. There is less postoperative nausea, vomiting, distention, and general discomfort than with any other type of anesthesia. It is best administered by the endotracheal method using the carbon dioxide absorption technic. The cost is still rather high, averaging $1.14 in a large number of cases, which figure, however, includes all accessory supplies. The advantages, however, outweigh this adverse item as it can be used in nearly all types of cases including many bad risks, and it almost entirely avoids the unpleasantness of ether. At the Mayo Clinic it is rapidly displacing ethylene,[10] which for several years has been rather extensively used. On the other hand, vinethene, which at first seemed to promise much as an inhalation anesthetic, has not maintained its popularity. While it is excellent for short anesthesia such as for the reduction of fractures or the extraction of teeth, being followed by prompt and complete recovery,[11] the reflexes are not easily controlled during the longer operations, and in addition the cost is rather high and the material relatively unstable. It is excellent as an induction agent preceding ether.

It is most gratifying to note the rapidly increasing use of basal anesthesia or narcosis; children present the ideal field for this type of premedication. They usually come to the surgery without their consent and often with their active opposition, frightened by strange surroundings and persons, mentally too immature to understand why they should be subjected to a painful or at best a disagreeable pro-

cedure, and although in some instances outwardly calm, inwardly so disturbed as to upset the endocrine balance completely. Gwathmey[12] very wisely states that the ideal condition of a child previous to operation is deep sleep and that the usual anesthetic methods, especially in tonsil and adenoid operations, are unsafe and inhumane. Children tolerate the barbiturates well in doses adjusted to age and size. Nembutal in over 1,200 cases has given highly satisfactory results. It should be given thirty to forty minutes before operation either by mouth or rectum, the patient moved with gentleness, supplemental ether induced by ethylene and oxygen and followed by carbogen until the throat reflex and respiration return to normal. Such a sequence and combination for tonsil operations is superior to the use of any one anesthetic agent alone as it results in a minimum amount of secretions, frequently no nausea or vomiting, a wider margin of safety between the therapeutic and toxic dose, and a postoperative period of quiet rest lasting from thirty to sixty minutes. It requires modern anesthetic equipment and should be under the supervision of a skilled anesthetist. This method may differ radically from the usual ones, but it carries the sanction of authority and is based upon an analysis of over 488,000 anesthetic records throughout the United States.

The barbiturates are of two classes, heavy and light, nembutal and sodium amytal being examples of the former, and evipal and pentothal sodium of the latter. The former objection to intravenous and rectal anesthesia that it is not controllable has been met by the light barbiturates.[13] They are used in dilute solution and are broken down and excreted with extreme rapidity. While the end products of the heavy barbiturates may be present in the excretions for seventy-two hours, those of the light type disappear so rapidly that only a bare trace remains in twelve hours, and for all practical purposes the effect has passed off in from three to thirty minutes, depending upon the dose. This characteristic places them definitely in the class of controllable anesthetics and hypnotics. Since the effect is upon the respiratory and not the cardiac centers, respiratory stimulants and artificial respiration can easily be used until the effect has completely disappeared, if there should be an instance of idiosyncrasy to the drug. They are usually administered intravenously and induction is smooth, pleasant, and rapid, unconsciousness being complete within one minute. Too rapid administration causes respiratory depression which is easily counteracted by coramine or picrotoxin. The dose for children is in proportion to the weight, based upon an average adult weight of 150 pounds. In a series of over 1,000 cases pentothal sodium was held to be slightly superior to evipal, the induction being smoother with less twitching, less fall in blood pressure, and no postoperative restlessness. It is from 30 to 50 per cent more potent than evipal and hence is more depressant to the respiratory center,[10] a characteristic which makes careful supervision particularly necessary in children. As a rule, however, children tolerate well the dosage appropriate to their weight.

The most recent development in basal anesthesia is the rectal use of the quick-acting barbiturates. Experimental investigation of evipal as a preanesthetic agent has shown that less supplemental anesthetic is required to produce anesthesia, more to produce respiratory failure and that the animals survive toxic amounts twice as long and have

fewer lung lesions than animals which do not receive this preanesthetic medication. Following these observations this method was used in 150 cases with most satisfactory results,[14] there being quiet sleep in over 80 per cent, an induction period of about five minutes, good relaxation, and little tendency to obstruction of the airway. It was much more satisfactory in abolishing psychic influences than morphine, which when used alone as a preanesthetic medication does not destroy them. The unfavorable comments were a rather slow postoperative reaction and a considerable amount of postoperative restlessness.

The intravenous use of evipal has been so extensively and favorably reported that further comment seems superfluous. In one series of 120 cases,[15] many children were included, one of whom was an infant eight months old in whom 140 mg. were used for a ten-minute anesthetic.

Until further reports upon the rectal use of the barbiturates are available avertin will continue to be the most popular and widely used drug for basal anesthesia by this route. The 100 mg. table is generally considered best for children[16] although less in tonsil cases is advocated by some observers. While it has been combined with morphine, atropine, and novocaine as total anesthesia in children,[17] its outstanding field is as a basal anesthetic.[18] The amount should be adapted to the condition of the patient, higher dosage being necessary in those patients who are nervous or frightened and in vigorous children or athletic individuals. Second doses for any reason should be used with extreme caution on account of cumulative effects upon respiration. Since the action on the liver is similar to that of chloroform, protection of liver function by preoperative intravenous glucose is advisable.

In all types of preanesthetic medication sufficient time should be permitted to elapse for the full physiologic effect to be obtained before the supplemental anesthetic is administered, as otherwise a combined action may occur with a rather alarming respiratory depression. Such depression yields readily to coramine by the intramuscular or intravenous route, depending upon the urgency of the condition. An experimental study of this action of coramine[19] has shown that it is a true physiologic antidote for the barbiturates, being distinctly superior to ephedrine or adrenalin,[20] which frequently have a rather serious secondary depressing effect. It is usually given intramuscularly but in urgent cases may be used intravenously in doses from 2 to 5 c.c. repeated every ten minutes until effective. In these large doses it occasionally causes hiccoughs, flushing and projectile vomiting, but these untoward symptoms are of short duration and leave no aftereffects.

The demand for preanesthetic medication and basal anesthesia has originated for the most part with the pediatricians and pediatric nurses rather than with the surgeons and anesthetists,[21] and the increasing use of these humane procedures will probably depend upon their tactful and persistent insistence.

For infants ether will perhaps continue to be the anesthetic of choice[22] although basal anesthesia may be used when indicated and nitrous oxide is valuable. Conservation of body heat is an important factor in this class of patients. The vague fear of thymus still per-

sists, but the continued insistence of Waldbott that the so-called thymic syndrome has an allergic basis seems gradually to be placing consideration of this troublesome condition on a more scientific foundation.[23] In the presence of an allergic family history skin tests with the proposed anesthetic agent or the administration of a small amount of it followed by a blood count for eosinophilia are of more diagnostic value than a roentgenogram.

Convulsions under ether anesthesia have been mentioned more frequently in the British than in American literature.[24] They begin with facial twitchings and dilated pupils, extend to the rest of the body, and if allowed to continue terminate fatally in over 30 per cent of the cases. They occur in toxic patients in whom there has not been opportunity for adequate preoperative preparation. The treatment consists in elevation of the head and the administration of 20 to 40 c.c. of 50 per cent glucose intravenously followed by 5 per cent glucose in saline.[25]

BURNS

An analytical study of the symptom-complex of burns shows that there is a rather constant sequence of events.[26] Pain and fright first induce reflex shock; loss of fluid from the circulation into the tissues begins at once and reaches a peak in about twenty-four hours, after which it gradually returns; bacterial contamination, which also occurs early, progresses to active infection and gives systemic evidence of toxic absorption in thirty-six to forty-eight hours. When this sequence is recognized, the rationale of treatment becomes apparent. Opiates and heat combat reflex shock; protection of the affected area from bacterial invasion if seen sufficiently early, and from absorption if later; maintenance of adequate fluid in the circulatory system. Fluid may be supplied by intravenous administration of normal saline solution even up to the amount of the normal blood volume, checking the amount by estimation of hemoglobin rather than the blood pressure[27] and the appearance of tissue edema. A hemoglobin of 125 per cent is not unusual, but, if it reaches 140 per cent, it indicates a concentration of the blood which is often fatal.[28] There is usually depletion of the blood chlorides but not of blood sugar, so glucose solutions are not indicated. Serum albumin, however, is lost and must be replaced by liberal blood transfusions if the administered fluid is to be kept in the blood vessels. In the absence of suitable donors gum acacia solution may be used, but blood is preferable. The large quantities of fluid necessary to maintain normal blood concentration are easily excreted when adjustment between tissue fluids and circulation takes place, and a reassuring sign is a transient polyuria. If edema develops, it usually indicates retention of chlorides, and the intravenous saline may be replaced by water if there is still blood concentration. An amount of sodium chloride equal to 0.5 to 0.8 gm. per kilogram of body weight in twenty-four hours is a reasonably safe standard.[29]

Protection of the burned surface by adherence to the principles of the tannic acid treatment is still fundamentally sound although many minor modifications are advocated by various writers. The addition of silver nitrate[30] as described by Bettman increases the speed of tanning, simplifies nursing, and reduces shock; mercurochrome forms a thin, transparent film through which any accumulation of pus easily

penetrates[31]; gentian violet is particularly effective against the streptococcus and is distinctly analgesic[32]; ferric chloride is stable in solution and forms a rather transparent coagulum which is elastic enough to permit early motion of joints, but the application is so painful that it should be preceded by liberal morphine or barbiturate analgesia.[33] The prime essential of the local treatment is protection from irritation, whether the irritation be from contraction of the surface due to air drying, from bacterial products, from frequent treatments, or from disturbing changes of dressings. The age-old principle of healing by rest applies as well to burns as to wounds.

A rather radical and novel departure in the treatment of the shock and pain incident to burns is the cold water treatment.[34] The pathologic changes in tissues injured by burning and by freezing are practically identical, and reasoning by analogy the initial treatment by application of cold should be as effective in one as the other. This is accomplished by immersion of the burned part, or the entire body, in cool water or by the application of cool wet dressings to burns of the face or small areas. Tap water at a temperature of 60° to 70° F. is used, the temperature being gradually increased to 80° F. during the first hour, to approximately 92° F. during the second hour, and to 98° F. during the third hour. The rate of increase is dependent upon the sensation of pain. The treatment is applicable to patients in the initial stage of shock soon after the accident. No attempt is made at extensive removal of clothing or devitalized tissue until after recovery from shock, when morphine is usually given and the area cleaned thoroughly, rinsed with sterile water, dried with a current of warm air and the usual protective measures instituted. The relief from pain and shock is spectacular. In a series of 52 cases the results were markedly superior to those in a preceding series of 130 cases treated by the usual antishock methods. There is no variation from the usual treatment of the various secondary local and general conditions, such as fluid administration, tannic acid, protection from contractures, skin grafting, etc.

The more recent studies of the circulation and the water metabolism associated with burns have changed the former concept that suppression of urine is due to toxic irritation of the kidneys. The anuria is known now to be due to lack of circulating fluid, and death occurs from that cause rather than from uremia. The absolute necessity of maintaining an adequate circulation is increasingly apparent.

INTRACRANIAL CONDITIONS

The fact that many cases of brain tumor progress steadily to a fatal termination has been responsible for the development of a rather fatalistic attitude, not only on the part of the laity, but also on the part of a considerable proportion of the medical profession. This is unfortunate, for the prognosis in some instances is good, and this attitude may in such cases prevent the early diagnosis and treatment which are so necessary to recovery. There is a fairly constant group of symptoms which to the alert medical attendant should suggest intracranial tumor, and a thorough neurologic analysis or a prompt reference to a neurologic surgeon will permit the institution of treatment which in many cases will be lifesaving. Suggestive symptoms[35] are vomiting, particularly of the projectile type which does not yield

to usual medical measures, persistent headaches, disturbances of vision, a tendency to clumsiness in play, falling or variations in gait, and disturbances of smell, hearing, or speech.

Children differ essentially from adults in the relative frequency of certain types of brain tumor; especially to be noted are the astrocytomas, the meduloblastomas and the adamantinomas. Astrocytomas may become cystic and in many instances be successfully removed. Meduloblastomas are often markedly relieved by operation or by roentgen therapy, but the relief is usually only temporary. Adamantinomas arise from the ducts of the hypophysis and cause disturbances of vision and pituitary dysfunction. They often respond satisfactorily to treatment. Lumbar puncture in cases of suspected brain tumor may be extremely dangerous. If there is clinical evidence of increased intracranial pressure, rest in bed, restriction of fluids, and dehydration by rectal administration of magnesium sulphate is a safe method of relief. The two symptoms to be kept constantly in mind by those who are in frequent contact with children are vomiting and persistent severe headache, as they occur in over 70 per cent of cases.

A condition which may closely simulate intracranial tumor is lead poisoning.[36] All of the usual symptoms may be present and to confuse the diagnosis further there may be absence of lead lines on the gums and of stippling of the red cells. However, roentgenography will usually show lines of increased density near the epiphyseal lines of the long bones and the blood, urine, and cerebrospinal fluid may show a positive lead test. Careful search will often reveal a source of supply of lead, such as paint from toys or water from the old type of lead pipes. Reduction of the intracranial pressure by dehydration methods or by surgical decompression relieves the symptoms and usually results in recovery.

An unusual and serious postoperative complication in infants and small children is intracranial thrombosis.[37] It occurs in clean as well as septic cases usually in the superior longitudinal sinus, and the onset varies from a few hours to two weeks after operation. Symptoms are convulsions, vomiting and delirium, or in some cases milder toxic symptoms. The cases reported occurred following operations for cleft palate, pyloric stenosis, and hernia. A report of eight cases of so unusual a condition is interesting and merits further study and analysis. It suggests the possibility that a careful search of the intracranial vessels might reveal this condition in some of those autopsies which have noted the cause of death rather vaguely as toxemia from postoperative infection, or postoperative shock. Convulsions of the jacksonian type with other localizing signs of an intracranial lesion may be due to an intracranial hemangioma.[38] The diagnosis is suggested by the presence of a nevus on the face or scalp on the same side. Such lesions are usually amenable to radium treatment. While multiple nevi of the skin are not uncommon, the suggestion that they may be associated with similar lesions within the body is logical and deserves careful consideration in the interpretation of an unusual symptom-complex.

CHEST AND LUNGS

In the treatment of empyema in infants and children certain concepts are generally accepted. These are that the mortality is highest in infants; that closed drainage is particularly adapted to infants;

that before the mediastinum has become stabilized or before the subsistence of the pneumonia, aspiration alone is permissible; that the variety of the infecting organism is a factor in determining the type of treatment; and that some form of open drainage either intercostal or by rib resection will be necessary in a large proportion of older children. A controversial point seems to be regarding the length of time aspiration should be used before resorting to open drainage. It is contended on the one hand[39, 40, 41] that open drainage at the appropriate stage of the process shortens the period of treatment, permits more efficient evacuation of purulent material, and relieves toxemia; and, on the other,[42, 43] that aspiration should be continued as long as the patient shows improvement, that complete evacuation of the pus is unnecessary, that fibrinous coagulums will undergo autolysis and disappear, and that open drainage should be delayed until there is insufficient response to repeated aspirations. It is difficult to reconcile these two views which seem to be in the nature of personal opinions. A comparison of mortality and morbidity is most unsatisfactory on account of the well-recognized fact that the severity of cases varies greatly in different localities and in different years in the same locality and by the fact that empyema is a localized collection of pus, the significance of which may be affected by diverse etiologic factors. Mortality and morbidity will be increased by a rigid adherence to any one method of treatment, and the highest degree of success will be attained only when there is the ability to evaluate the signs and symptoms and the judgment to use the method of treatment which is adapted to the type and stage of the pathologic process. In other words, the best mortality statistics over a long period of years will be obtained by those who have a thorough knowledge of the fundamental pathology of the condition and of the various methods of treatment. Such a statement is so self-evident that it would seem almost puerile, but repeated emphasis on fundamental principles would seem indicated when one considers the great numbers of articles which are continually appearing stressing some one method of treatment as responsible for good or bad results and failing to evaluate or to correlate other important factors which have equal or greater significance in an analysis of end-results.

Bronchoscopy and esophagoscopy require special training and teamwork, and the symptoms indicating the use of these procedures should be widely known.[44] A foreign body in the trachea or bronchus causes one or more of the following symptoms: choking, gagging, coughing, wheezing heard more distinctly at the mouth than over the chest wall, hoarseness, and cyanosis. These symptoms appear at varying periods after the foreign body has entered the air passages: nonobstructive metal objects may give few signs for several weeks, whereas vegetable substances usually set up violent reactions at once with cough, toxemia, and irregular fever. When the foreign body has been lodged in the lungs for some time, it may cause bronchiectasis, lung abscess, massive collapse of the lung, unexplained dyspnea, or symptoms suggesting tuberculosis with persistent absence of tubercle bacilli. In the presence of such findings a bronchoscopic study is indicated. Roentgenography may fail to show the foreign body, but its presence may be suspected if there is a constant area of increased density, often lobular in its shape and distribution.[45] A movable object in

the trachea may produce a snapping sound by being alternately drawn down to the bifurcation and blown up against the larynx.[46] If such an object is in one of the bronchi, it may act as a valve permitting the entrance but not the exit of air, and producing an obstructive emphysema with a high pitched percussion note and hyperresonance. Fluid secretions due to the irritation of a foreign body follow the laws of gravity, and this fact should be remembered for the purpose of postural drainage and in the endeavor to prevent fluid from entering the unaffected lung.

Foreign bodies in the esophagus often lodge behind the cricoid cartilage causing pain on swallowing and a sensation of pressure which may be referred to some point at a distance from the lesion.

Bronchoscopy permits accurate differential diagnosis instead of "inferential diagnosis"[47] in many conditions affecting the air passages in infants and children; among which may be mentioned especially asphyxia neonatorum, congenital atelectasis, congenital anomalies of the larynx, thymic compression of the trachea, and acute and chronic suppurative diseases of the respiratory system. The personnel of the modern obstetric hospital should include a bronchoscopist and every obstetric department should have available the services of some one sufficiently expert to examine the larynx and upper trachea of infants.

Diaphragmatic hernia in infants and children is being reported with increasing frequency, and the operative treatment shows a good percentage of satisfactory results. The operation should be performed early because the diaphragm is a muscular structure and its development is dependent upon function.[48] When its activity is diminished or prevented by a hernia, normal development during the period of growth is impossible, resulting in disturbances of digestion, respiration, and circulation which give the typical picture of malnutrition and lowered resistance. Following successful operation, there is a rapid return to a normal state of nutrition, rate of growth, and physical activities. The condition in some instances causes few symptoms, and the diagnosis may be made only as a result of a careful general examination including roentgenography of the chest to determine the cause of slow gain in weight and vague respiratory symptoms. In other instances feeding difficulties, dyspnea, small abdomen, and full tympanitic chest indicate the diagnosis so definitely that the roentgenogram is merely confirmatory.[49] The operation presents certain technical difficulties which places it clearly in the domain of major surgery. It is best done under positive pressure anesthesia. The replacement of the ectopic viscera may be difficult on account of size, number, or adhesions; the line of closure of the diaphragmatic opening may stretch or open postoperatively; or there may be associated congenital anomalies.[50] A condition which may be confused with diaphragmatic hernia is congenital elevation of the diaphragm sometimes mistakenly called eventration.[51] In this condition there is no enlargement of the normal diaphragmatic openings, the diaphragm being intact and thinned out into a translucent fibrous sheet, and the abdominal viscera do not pass into the true thoracic cavity. A careful roentgenographic study will show that while the viscera are above the normal position of the diaphragm, their relations are more constant than in hernia; they do not pass through a diaphragmatic open-

ing; and the shadow of the diaphragm cannot be seen, or is much less distinct than in the case of hernia. The differential diagnosis is important as surgery is not indicated, and if the infant survives the first few months the condition is not incompatible with long life.

Atresia of the esophagus with the usual accompaniment of tracheoesophageal fistula is so uniformly fatal that a suggested procedure for treatment is interesting.[52] The diagnosis is not difficult but is sometimes delayed until aspiration pneumonia has occurred. There is excessive mucus in the mouth from accumulation in the blind esophageal pouch. The lower segment is the one which usually communicates with the trachea and the gastric secretions, the production of which is stimulated by attempts at feeding, regurgitate into the lungs causing cyanosis and dyspnea with the coughing up of quantities of frothy fluid. This causes marked prostration, and the infant appears almost lifeless but gradually recovers only to repeat the same performance at the next feeding. Death is due to starvation and dehydration if it does not occur earlier from accumulation of fluid in the lungs. When the condition is suspected, a catheter may be passed very gently into the throat until it meets the obstruction, and the mucous contents of the pouch withdrawn to prevent aspiration. When the obstruction is well below the level of the larynx, lipiodol may be injected and the condition visualized by roentgenography. Barium should never be used as it is irritating. Immediate surgery is indicated and consists of tying off the cardiac end of the esophagus with tape to prevent regurgitation of stomach contents, followed by gastrostomy to permit feeding. The esophageal pouch must be kept clear by aspiration. Later the pouch may be brought out to a subcutaneous position and a skin tube prepared to construct an anterior thoracic esophagus. The many technical difficulties of this series of steps are so apparent that for the present it will have mainly an academic interest and should be attempted only in an institution having extensive equipment and the services of a highly skilled staff.

GASTROINTESTINAL TRACT

The medical literature on appendicitis continues to be voluminous, and there is little to distinguish that of the past year from that which has been previously reviewed in this department. Occasional articles stress the value of cooperation between the pediatrician and the surgeon, the necessity for a careful, unhurried examination, the evaluation of the reactions of the individual child, and appreciation of the anatomic and physiologic differences between children and adults.[53-57] Much information may be gained by a quiet inspection after the abdomen is uncovered, noting posture, activity, respiration, and facial expression. The child with an acutely inflamed appendix protects the tender organ by lying quietly and avoiding changes of intraabdominal pressure or tension, such as are caused by unnecessary movements of the legs or trunk or the abdominal type of respiration. His expression is apprehensive if he anticipates an attempt to touch the abdomen. Quiet inspection while obtaining the history also gives the child time to inspect the examiner and gain confidence so that palpation of the abdomen beginning on the side which is not tender seems only a continuation of the conversation. Time is necessary also to obtain the child's confidence after a thoroughly bad psychologic attitude has

been quite effectively produced by repeated assurances on the part of the family that the doctor will not hurt him. It is regrettable that statements occasionally appear to the effect that rectal examinations are of doubtful value. While it is, of course, true that rectal examination is not to be considered a fixed and unvariable part of the diagnostic procedures, its value should not be minimized. It may be unnecessary or merely confirmatory for the keen, trained pediatrician and definitely contraindicated for the examiner whose finger is large and whose methods are brutal, but there still remains a great proportion of cases in which definite and valuable information may be obtained in this way, and especially is this true in infants and small children.

The position of the appendix in children is variable and often quite different from the usual adult location, a fact to be remembered when the point of maximum tenderness is on the left side, in the midline, at the edge of the liver, or in the lumbar region. A retrocecal appendicitis may be indicated by frequent loose or mucous stools and may give none of the usual signs of peritoneal irritation. In certain parts of the country symptoms suggestive of appendicitis but accompanied by bloody or mucous stools may indicate amebic or bacillary dysentery,[58, 59] and operation is definitely contraindicated. There may be the usual pain, tenderness, and temperature of appendicitis, but there is usually little or no rigidity or leucocytosis, and there are often eosinophilia, spasticity of the colon, palpable mesenteric lymph nodes, and a positive stool culture. When the differential diagnosis is difficult and there is the possibility that the symptoms may be due to an extraabdominal condition, the fact that the blood sedimentation time in acute appendicitis is usually normal may be of distinct assistance.

In definitely doubtful cases it is better to perform an occasional unnecessary operation than to lose a life on account of delay.[60] This advice, however, is not to be confused with the recommendation still too frequently seen that appendicitis should be operated upon as soon as the diagnosis is made, regardless of the stage of the pathologic process. Such practice results in unnecessary mortality when the operation is performed during the danger period between the second and the seventh day, the period of dehydration, carbohydrate depletion, toxemia, and negative phase of bacterial resistance. If adhesions have not formed and there is evidence of peritonitis, it is difficult to comprehend the conception that the protective activities of the peritoneum can be aided by operative trauma. The first ten hours is a relatively safe period, but after this time the postoperative mortality rises steadily to a peak on the fourth and fifth days[61]; analysis of the mortality statistics cited by those who advise immediate operation regardless of the stage of the pathologic process will usually show this well-defined danger period. The conviction is steadily growing that children seen after the second day of symptoms show a definitely lower mortality rate under the nonoperative treatment than following immediate operation. If there is evidence of abscess formation, it is better to allow time for a definite wall to form rather than to attempt early drainage.[62] During the two or three days required for this process, the general condition of the patient may be markedly improved by appropriate measures.

Conditions which are often impossible to differentiate from acute appendicitis are acute regional ileitis and mesenteric lymphadenitis,[63, 64, 65] the diagnosis in most instances being made only after the abdomen is opened. Ileitis usually occurs in older children and adolescents and is characterized by marked, hyperemic thickening of the terminal portion of the ileum involving the wall of the bowel rather than the mucosa and accompanied by extensive lymphadenitis of the mesenteric glands. The glands may suppurate, and there may be local gangrene of the bowel wall with perforation and peritonitis. The appendix often shows little or no involvement, and the temptation to remove it should be resisted unless it is acutely inflamed. If, however, the process appears to be chronic, the appendix may be removed but it is unwise to invert the stump, and, in general, surgical procedures should be reduced to a minimum. Both conditions seem to be secondary to infections of the upper respiratory tract, and if tonsillar infection is present, a subsequent tonsillectomy is advisable. When the mesenteric adenitis is the predominating condition, the enlarged glands may in some instances be palpable during periods of relaxation in abdominal rigidity. There is usually a history of repeated attacks of mild abdominal pain, and vomiting is not as constant a symptom as in appendicitis. In general it may be said that mild symptoms, general rather than sharply defined local tenderness, cervical adenitis and an upper respiratory infection are more suggestive of mesenteric lymphadenitis than of appendicitis, but it is safer to operate and find only an adenitis than to miss the diagnosis in acute appendicitis.

However subject to criticism the term chronic appendicitis may be, a condition characterized by irregularly occurring abdominal pain, digestive disturbances, changed disposition, and interference with nutrition is occasionally encountered which is completely relieved by the removal of the appendix. Appendices removed under these circumstances and occasionally those removed during abdominal operations for other conditions will often show under careful special methods of staining definite nerve lesions consisting of hyperplasia of the nerve tissue in the mucosa or localized neuromas,[66] which may well cause reflex disturbances of digestion and pain referred to other parts of the abdomen.

It has been frequently emphasized that early diagnosis of intussusception is a prime factor in successful operative treatment and that early diagnosis depends upon both the profession's and the laity's becoming intussusception conscious. The most suggestive symptom is severe, intermittent, colicky pain in a strong, previously well baby. The infant shows pallor and the appearance of shock during the attacks but at first appears normal and happy between attacks. The severity of symptoms increases, and the characteristic sausage-shaped mass appears in the upper abdomen together with scanty mucous stools tinged with blood. When the diagnosis is made early, reduction can be accomplished in about 50 per cent of the cases by rectal injection of normal saline solution. In a series of 210 cases the average duration of symptoms in cases which yielded to this treatment was sixteen hours[67] while the average duration of those which could not be so reduced was thirty-one hours. All preparations for operation should be made and the infant anesthetized. With the container at a height of three and a half feet the solution is allowed to run in

slowly for three or four minutes, then is expelled, and the injection is repeated a second and third time. The appearance of flatus is a reasonably sure indication that reduction has taken place. Another indication of reduction is an increase of 1½ to 2 inches in the circumference of the abdomen which does not disappear with the return of the solution. This increase is dependent upon the passage of some of the solution through the ileocecal valve and is determined by measuring the abdomen before and after reduction. If there is doubt as to whether reduction has been accomplished, a small incision should be made and the abdomen should be explored. In cases where a confirmatory operation is not done, satisfactory evidence of reduction may be obtained by administering a teaspoonful of powdered charcoal before the child leaves the table. The charcoal may be recovered by enema about four hours later. Hipsley has not found the use of barium under fluoroscopic observation of any advantage over saline. When barium is used, reduction can be observed and its progress assisted by kneading and massage during the introduction of the enema.[68] This procedure is probably safer in recurrent intussusception than in the usual acute type on account of the temptation to be too vigorous when progress becomes slow and the eye is not able to determine the condition of the bowel wall.

Irreducible intussusception is encountered more frequently in older children and in the ileac type, in whom the symptoms are more likely to be indefinite and the diagnosis delayed. There is usually vomiting without fever, abdominal rigidity or distention and a somewhat tender abdominal mass can be felt.[69] In four such cases the bowel was gangrenous, all patients recovering after resection or lateral anastomosis. The intussusception passed in one instance and was apparently absorbed in two. There is no tendency to peritonitis or hemorrhage when the bowel is left in place following lateral anastomosis; therefore procedures such as splitting the bowel with removal of the intussusception, enterostomy, or exteriorization are not favored. A record of four consecutive recoveries from this very serious condition is unusual to say the least, a factor being perhaps the age of the children, two and one-half to twelve years.

Intussusception may be initiated in later life by a Meckel's diverticulum which has caused intestinal hemorrhage and pain in childhood suggesting gastric or duodenal ulcer.[70] If a careful roentgenographic study fails to reveal a gastric or duodenal ulcer or no other cause can be found for gross or occult blood in the stool a Meckel's diverticulum should be considered present. It may not be visualized following ingestion of barium because the entrance is so directed that intestinal contents rarely enter. The diverticulum should be removed at a time of choice because of the ever present danger of perforation, hemorrhage, or intestinal obstruction.

Persistent vomiting during the first few days of life usually indicates atresia rather than pyloric stenosis. When the atresia occurs in the duodenum the vomitus may contain bile and after the first few hours usually contains blood. The blood is thought to come from mucosal vessels ruptured by the extreme gastric distention and peristalsis. The diagnosis is easily corroborated by the roentgenogram which shows a dilated stomach and duodenum with absence of gas in the intestine. The defect is often associated with other anomalies,

such as malrotation of the intestine, fetal type of mesentery, multiple atresias, and fetal position of the cecum.[71, 72] Early operation has not given as good results as when it is delayed for one or two weeks, nutrition being maintained by intravenous or rectal injections.

Early jaundice which grows progressively deeper is usually due to a congenital obstruction of the bile ducts[73] either by a plug of mucus or bile or from atresia. The presence of bile in the stools or urine is no evidence of patency of the ducts as it may be excreted from the blood in sufficient quantity to give positive tests. Other conditions which cause early jaundice are icterus neonatorum, erythroblastosis, and hemolytic icterus, in all of which the diagnosis becomes apparent within a few days, whereas the jaundice due to a congenital obstruction is not associated with other symptoms or signs but continues to increase gradually. There is no harm in waiting for a month or two if necessary to rule out other conditions, and to improve the nutrition of the infant. The operation may be performed at the age of three or four months, although one child in a series of forty-five cases lived for a year before operation. At operation the obstructing plug may be dislodged by distending the duct with saline solution, or in cases of atresia an anastomosis with the duodenum may be possible. When there is atresia of the hepatic duct, the results are not as satisfactory as when the common duct is involved. In only about one-third of the cases was the condition suitable for surgery, and of these, 60 per cent recovered. If the ducts are patent, a complete absence of the gallbladder and cystic duct may cause no symptoms and be discovered accidentally.[74]

An interesting observation with a possible bearing upon Hirschsprung's disease has been recorded in the case of a young adult having a stricture of the anus due to a burn in infancy.[75] Typical symptoms of the disease gradually developed, and operation at the age of seven and one-half years to relieve the stricture failed to affect them. Several years later a sympathectomy was completely successful. The interesting point is the possible effect of long-continued irritation of the anal nerve endings upon the neuromuscular mechanism of the large bowel and whether it may suggest a possible cause of Hirschsprung's disease. Treatment by section of the sympathetic nerves is more satisfactory than bowel resection because it is productive of less shock, permits shorter hospitalization, and is physiologically more rational. It is preferably done during childhood before faulty bowel function has become too thoroughly established.[76]

In the diagnosis of intestinal obstruction or of ileus, roentgenography gives valuable assistance, permitting recognition of the condition before clinical symptoms have advanced to a point where surgical relief is difficult.[77] Gas and liquid levels can be seen in the upright or side positions and give an indication of the location of the obstruction. They are more marked in strangulation obstruction than in the simple type. Moderate general distention is seen normally in children under the age of two years and is rather common after any abdominal operation.

Chronic duodenal ileus is a condition in which the attempt to obtain relief by surgery is usually unsatisfactory.[78] It is characterized by marked gastric and duodenal distention, vomiting, gastric retention, anorexia and malnutrition and may persist for several years. It is usually due to compression of the duodenum by a peritoneal band or

by the root of the mesentery containing the superior mesenteric artery, in which case surgery can accomplish nothing. In the newborn it is to be differentiated from duodenal atresia by the fact that a thin trickle of barium will be seen to pass gradually through the obstructed region, and the same method in older infants will rule out pyloric stenosis, the opaque medium passing readily into the duodenum. Treatment by gastric lavage with 1 per cent sodium chloride at twelve-hour intervals for several days usually gives marked relief. The interval may then be lengthened to two or three days for about three months, but if distention and vomiting recur the more frequent washings must be resumed. Most cases improve under this treatment and the improvement tends to become permanent at about the age of eight years.

The possibility of duodenal ulcer should be considered if an infant or small child has a history of digestive disturbances and chronic, vague, recurrent pain in the abdomen.[79] There may be occasional vomiting and the passage of blood by bowel. Perforation may occur, giving symptoms of shock, with marked epigastric rigidity and tenderness without distention, and operation should be performed at once. When perforation occurs in the newborn the diagnosis is difficult and is rarely made except at autopsy.

Perforation of the jejunum may occur as a result of trauma.[80] Suggestive symptoms are steadily rising pulse rate, vomiting, local or general rigidity, and severe persistent abdominal pain, although in some instances pain is absent in the early stages. There is not usually a great escape of intestinal contents on account of the reduced peristalsis and the eversion of the mucosa, and the presence of shifting dullness is much more indicative of massive hemorrhage from torn mesenteric vessels than of intestinal contents. No operative procedures should be instituted until the initial shock has been relieved.

While it is well known by the profession that most swallowed foreign bodies pass spontaneously, it will no doubt be a relief to many a distracted mother to know that in an observed series of 849 cases this occurred 818 times and that the mere presence of a foreign body in the stomach is not an indication for removal.[81] Among the few objects which may require surgery may be mentioned radium, bodies so long that they cannot pass the angles of the duodenum, and a matted mass of several articles. The progress of any ordinary object can be checked by roentgenography, and gastrotomy should be performed only if the object cannot be removed by gastroscopy or if it seems unsafe or otherwise inadvisable to allow it to remain.

OTHER ABDOMINAL CONDITIONS

In early suspected peritonitis or when it is desirable to obtain definite information regarding the causative organism or probable source of the infection diagnostic aspiration of the abdomen is a valuable aid.[82] There is little danger of injuring the intestine if the puncture is made below the level of the umbilicus using an ordinary spinal needle with an obtuse bevel and if the point of the needle is turned to lie parallel with the parietal peritoneum as soon as it is felt to enter the abdomen. When the amount of peritoneal exudate is small, it is usually more easily found against the parietal peritoneum, and often only a drop or two is obtainable. A smear and culture should be made, of which the former is more essential for immediate diagnosis.

The failure to obtain fluid should not be considered as evidence against the presence of peritonitis or permitted to outweigh other clinical evidence, but a positive result gives a definite basis upon which to outline treatment. "One may dispute about symptoms, but one cannot take issue with a drop of pus containing great numbers of cocci." It is particularly to be emphasized that a positive finding is rarely, if ever, to be used as an indication for laparotomy for the surgical treatment of peritonitis is productive of higher mortality than the nonsurgical. The value of the procedure lies in the information which it gives as to the causative organism and the consequent ability to institute appropriate specific measures. Particularly is this so in the early diagnosis of pneumococcal peritonitis.

When peritonitis is found upon opening the abdomen, stimulation of the reticuloendothelial system by peptone broth has resulted in a high percentage of good results.[83] In a series of 43 cases including several children, there was but one death. This occurred in a ten-year-old child who developed an acute perforating appendicitis during the early stages of an attack of influenza and died on the fourth postoperative day from a generalized infection. Of the 42 cases with recovery one was complicated by bronchopneumonia, and two were complicated by mild symptoms of ileus which cleared up easily. Any treatment of peritonitis which results in uneventful recovery in 39 out of 43 cases and a mortality of only 2.3 per cent deserves careful consideration, even though the series of cases is comparatively small. The solution is made by diluting commercial peptone broth with normal saline, and it is freely introduced into the peritoneal cavity at the time of operation.

Inguinal hernia in infants is not particularly uncommon, but in premature infants it may be serious. In a study of forty-four such cases there were six instances of strangulation or incarceration.[84] Such an occurrence is an indication for immediate surgery regardless of age. It is especially important that when a hernia exists any cause of increased intraabdominal pressure should be relieved. Among these may be mentioned excessive crying, vomiting, straining at stool, and phimosis. In seven infants early circumcision so reduced the straining that the hernia disappeared. Truss treatment is likely to be ineffective if the causes of straining are not first relieved.

With the exception of diabetes, pancreatic lesions are rare in children. That they may occur, however, is evidenced by a report of a primary carcinoma of the pancreas in a fourteen-year-old boy.[85] The usual cachexia of malignancy gradually developed, but there was nothing else to suggest the diagnosis, and the case is mentioned here simply on account of its extreme rarity. Acute pancreatitis, however, is occasionally encountered,[86] giving symptoms of acute onset with severe abdominal pain, persistent vomiting, general abdominal tenderness often without rigidity, and systemic symptoms of shock. The urinary diastatic index is usually high. The condition may follow a septic process elsewhere in the body, and surgery is suggested for the drainage of pancreatic ferments and blood-stained fluid. It would seem wise to refrain from surgical intervention except on very definite indications of abscess formation or peritoneal irritation under which circumstances the preliminary preparation of a drainage tract walled off from the peritoneal cavity is a valuable procedure. Children re-

cover slowly from such upper abdominal surgery and, wherever possible, conservative treatment results in a shorter period of convalescence.

Multiple hemangiomas of the liver causing fatal pulmonary edema are reported in a three-month-old infant.[87] The enlargement of the liver and abdomen was accompanied by vomiting and constipation, and there was a small elevated hemangioma on the right side of the chest. Earlier in this review[38] reference has been made to the possible association of hemangiomas in the underlying organs with similar superficial lesions, and in this case such an association was suggestive in explaining the symptoms.

Abdominal cysts arising from various structures usually cause symptoms by pressure upon adjacent viscera after a gradual painless enlargement of the abdomen. The more common forms are omental, ovarian, mesenteric and enteric, or enterogenous cysts.[88, 89, 90] Diagnosis is often difficult and requires a most careful study including such aids as gastrointestinal and renal studies and aspiration, the final step usually being exploratory laparotomy. A suggestive symptom in cases of enterogenous cysts is pain associated with the taking of food. Mesenteric cysts attached near the intestine occasionally cause intestinal obstruction.

Splenectomy is of proved value for certain conditions which are encountered in childhood, and the indications are reasonably clear.[91] They are, first, to stop a perverted activity of the spleen; second, to check the progress of some obscure pathologic process; third, to relieve the body of an organ grossly enlarged and useless; and fourth, to remove a focus of infection. The best results are obtained in hemolytic icterus and purpura hemorrhagica. In splenic anemia and splenomegaly with gastric hemorrhages results are good when the anemia is associated with leucopenia but not when there is leucocytosis. In sickle-cell anemia there is usually an improvement in symptoms but not in the blood picture. The large size of the spleen in erythroblastic anemia causes so much discomfort that splenectomy often gives welcome relief, but the progress of the disease is not affected. Erythroblastosis of the newborn which does not yield to transfusions has apparently been cured in some instances by splenectomy. In hemolytic icterus it is unwise to undertake splenectomy during a crisis. The operation should be deferred until the red cells and hemoglobin have returned to a reasonably good level.

ORTHOPEDICS

Osteomyelitis causes as great a degree of disability, crippling, and invalidism as tuberculous joints or infantile paralysis, and on account of its serious nature should be equally feared. Early diagnosis is as essential for adequate treatment as in appendicitis, a fact which should be constantly in the minds of the profession and of the laity. The importance and significance of the usual symptoms of appendicitis have been so emphasized by leading surgeons that the general public is becoming appendix-conscious and a similar condition must be brought about if the serious secondary results of osteomyelitis are to be avoided. To this end the dictum should be: Any child under thirteen years of age with pain in an extremity, loss of function, fever, and leucocytosis has acute osteomyelitis until proved otherwise.[92] It is essentially and, in the hematogenous form, almost exclusively a dis-

ease of infancy and childhood, and the responsibility for early diagnosis rests upon the general practitioner or pediatrician who first sees the child. Too often the orthopedic surgeon is called to treat the sequelae of neglect: bone necrosis, multiple metastases, fracture, deformity, secondary contractures, and interference with bone growth, with the associated anemia and parenchymatous and cardiac lesions. The visible and palpable signs of inflammation are usually absent at first, with the exception of local tenderness, and there is often a history of previous otitis media or boils. The joints are rarely involved except in older children where the epiphyseal cartilage is thinner and the infection penetrates more easily, making the disease progressively a more urgent and serious problem with the increasing age of the child. In differentiating osteomyelitis from arthritis, it is to be remembered that an infected joint cannot be moved without pain, whereas, when the process is near a joint, painless motion is possible if due care is exercised.

The osteomyelitis of infants differs distinctly from that of older children.[93] The bones are softer, with larger cancellous spaces, and the periosteum is more closely attached. This permits infection to pass more readily through the cortex to the subperiosteal space with more frequent formation of a subperiosteal or soft tissue abscess. In such instances it is often unnecessary to make an opening through the cortex. There is more rapid formation of bone than in older children and with reasonably early drainage there is rapid healing with rare formation of sequestrums. Care must be exercised in choosing the time for drainage as the general condition of the infant is of first importance and a delay of two or three days especially in streptococcic infection may be required to develop an extremely necessary resistance. Such a delay does not necessarily mean a bad result in an infant, whereas too early operation is dangerous. Drainage should be thorough, the wound packed with vaseline gauze, the part immobilized and the local condition left strictly alone for at least one or two weeks. The more infrequent the dressings, the more rapid the recovery in the average case. In older children it is to be remembered that the bone infection is usually a local manifestation of a general process, and operation before the development of general resistance may add the shock of operative trauma to a defense mechanism which is struggling to overcome a septicemia.

The highest mortality occurs in those patients operated upon during the first week of the disease, but nice judgment is necessary as to the time of election for operation, because too much delay favors the formation of multiple foci.[94] As is true with appendicitis, treatment should be based on a knowledge of the pathologic process and an inflexible rule as regards time of operation may usually be considered evidence of a lack of that knowledge. Early operation regardless of positive blood culture or number of areas involved is at times advised in older children, but this may be followed by secondary hemorrhage seven to ten days later. This is a serious complication requiring blood transfusions.[95] In older children when the disease has become firmly established, recurrences are not uncommon, and it has been suggested that in reporting series of cases a terminology similar to that used in analyses of cancer would be desirable, listing cases as five-, ten- or fifteen-year cures.

During the operation it is necessary to keep constantly in mind the characteristics of septicemia, such as the formation of bacterial emboli or of septic thrombi and the effect of toxemia on other organs and on the child as a whole. The location of an embolus or thrombus in a terminal capillary or in a large vessel will determine the amount of bone destruction; rough operative manipulation such as curetting the medulla, the indiscriminate use of chiseling instead of motor-driven instruments, too vigorous gauze sponging, etc., tends to dislodge infected material and favor the formation of multiple secondary lesions especially when general resistance has not yet developed,[97] and the same result may be produced in a lesser degree by too frequent postoperative dressings and lack of immobilization. The value of the Orr treatment may be due in some measure to the formation of a bacteriophage. This suggests the use of stock bacteriophage and excellent results are reported in traumatic primary osteomyelitis of the phalanges following such treatment, frequent injections being used.[98] Staphylococcus antitoxin is recommended if the blood culture is positive, as free circulating toxin has been demonstrated and is a cause of hemolysis.[99] The blood serum of normal adults usually has a high titer, and a transfusion from a person who has recovered from a staphylococcic process supplies a serum of particularly high titer. Such treatment is, of course, not necessary after the blood stream has become sterile and the process has become definitely localized in the bone. Stimulation of the reticuloendothelial system by the use of peptone broth packs, as referred to earlier in this review under the treatment of peritonitis, has been found effective and has interesting possibilities. The use of maggot therapy, although still rather frequently reported,[100] is apparently being supplanted by less discomforting forms of treatment and is being restricted to those conditions requiring removal of necrotic tissue or stimulation of healthy granulation,[101] and again the necessity of judgment and the application of measures based upon a knowledge of the pathologic stage or individual condition rather than the use of routine treatment are emphasized.

In the consideration of postural defects a careful distinction is necessary between the accentuation of normal physiologic curves seen in the earlier years of life and pathologic conditions which are precursors of later deformities.[102] As examples of the former may be mentioned early bowlegs, knock knee and lordosis which should be kept under observation but usually become normal under a proper dietary and hygienic regimen. Flat feet, round shoulders, winged scapulae, and scoliosis, however, belong in a different category and may develop into serious deformities unless recognized and subjected to vigorous and well-supervised treatment, such as corrective shoes, exercises, muscle training, braces, casts, or operative procedures. It is not sufficient to advise parents that children need more out-of-door exercise or should be encouraged to play more. Definite instructions must be given, specific exercises detailed, and periodic supervision required over a sufficiently long period to be sure that the desired results are obtained, a period of observation of two to four years often being necessary.

The effect of ultraviolet radiation upon the healing of bone has been the subject of so much diverse comment, and so much loose information has been disseminated by commercial firms to both the profession

and the laity, that a course of animal experimentation was undertaken to clarify the situation.[103] Treatment by means of carbon arc radiation was used in a carefully controlled series of fractures. The period of bone healing was slightly improved, averaging between 5 and 10 per cent less in the treated cases than in the untreated controls; no correlation could be determined between the healing of fractures and the calcium-phosphorus ratio in the blood serum; and healing was definitely retarded by the type of radiation which produced vasodilation, confirming the results following vasodilation produced by sympathectomy.

Fractures about the elbow are rather common in children, and good ultimate function is more dependent upon careful reduction than in fracture of the shaft of long bones, where growth tends to compensate for shortening or moderate deformity.[104] Complete anesthesia and early reduction are essential, and open reduction may be necessary, particularly in fracture of the lateral condyle of the humerus.[105] This fracture is often unrecognized and if unreduced goes on to deformity from irregular growth which may not become apparent until later years. Careful physiotherapy gives excellent results, it being particularly important to avoid forced or vigorous passive motion, to use massage and heat as early as possible, and to encourage active motion as soon as it is safe.[106]

The adolescent period is characterized by a rapid increase in weight and muscle power, which often outstrips the ossification of the epiphyseal lines and results in a number of rather characteristic lesions. Participation in athletics involves falls and sudden muscular exertion which put such strain upon these regions that epiphyseal separation frequently occurs. When the medial epicondyle of the humerus is torn away, it may be drawn downward into the elbow joint by the flexor pronator group of muscles, causing limitation of motion and tenderness at the point of fracture.[107] Open operation is necessary in practically all instances and gives excellent results, whereas disability, limitation of motion, and possible injury to the ulnar nerve occur if the fragment is not replaced. Avulsion of the epiphysis of the lesser trochanter is also caused by direct muscle pull, giving symptoms of generalized pain throughout the entire thigh, local tenderness, and rather marked muscle spasm, which limits all motions of the hip except adduction.[108] The remaining insertion of the muscle prevents any distinct degree of displacement, and fixation in a short spica gives good results, walking with crutches or cane being permitted in one week and the plaster being removed in four weeks.

Slipping of the capital epiphysis of the femur, which also occurs most frequently at this period, is apparently due to trauma and muscle tension, possibly combined with rapid increase in weight.[109] Microscopic study has shown that this condition is not associated with rickets or osteomalacia but that the lesion consists of a fracture through the epiphyseal plate including a small portion of the adjoining osseous tissue. As noted in this review last year, the degree of disability varies with the degree of displacement; bed treatment is always necessary; open operation may be required; and results are not particularly satisfactory, shortening and limitation of motion being not uncommon sequelae.

Avulsion or displacement of the tibial tubercle with occasional frag-

mentation—Osgood-Schlatter's disease—gives symptoms of local pain, tenderness, and swelling with limitation of motion[110] and requires immobilization with application of heat until the acute symptoms subside. This should be followed by elastic pressure for several weeks and complete healing may require two or three years. Recovery is more rapid if immobilization by splint or plaster is continued four to six weeks.

A sacroiliac syndrome occurring during adolescence is thought to be due to changes in the sacroiliac region resembling those seen in Osgood-Schlatter's disease or in Legg-Perthes' disease.[111] Roentgenographic studies of normal individuals show that the sacroiliac space is wider in children than in adults and that epiphyses develop about the fifteenth or sixteenth year. Symptoms of low back strain appear in children who engage in vigorous activities, the initial injury often being so slight as to escape notice. Forward bending and lateral bending to one side are limited; straight leg raising from a lying position is much restricted and causes severe sciatic pain; there is localized tenderness over the affected sacroiliac region; and there is a limp characterized by a short-stepping gait on the side involved. Without treatment the condition tends to improve gradually but recurs on very slight strain. The best results are obtained by support and protection with restriction from athletics for at least one year.

Congenital dislocation of the hip in infants is successfully reduced in about 80 per cent of cases by fixation in a position of extreme abduction.[112] This places infants in a special class as regards this condition and imposes upon the obstetrician and pediatrician the obligation of early diagnosis. On account of the rounded contour and usual position of flexion of an infant's thighs the usual signs of shortening, absence of the head of the femur from the acetabulum upon palpation, and limitation of abduction from a position of right-angle flexion may easily be overlooked. For that reason special attention should be paid to the hips in the examination of all infants. When facilities are available and in all cases of doubt, a measurement of the acetabular angle is valuable. This is shown on the roentgenogram by drawing a base line through the lowest points of the iliac bones in the acetabular fossae and a line from the upper outer pole of each acetabulum through this lowest point of the iliac bone of the same side. It is essential in taking the roentgenogram that the tube be centered exactly over the middle point of the upper border of the pubis. The angle formed between this oblique line and the base line has been called the acetabular index,[113] but as it is read in degrees it is not a true index and should more properly be called the acetabular angle. In the normal newborn infant this angle averages 27.5 degrees. If it is greater than 30 degrees, there is either an actual or potential dislocation of the hip, and the thigh should be maintained in marked abduction until the acetabulum and head of the femur have become adjusted to each other, and there is clinical evidence of stability. The average acetabular angle as determined by a study of normal children three years of age was 20 degrees, and in children two years of age with congenital dislocation of the hip it was 37.5 degrees.

In older children conditions vary so widely that treatment must be individualized. In general, manipulative reduction is not successful after the fourth year, but it should be attempted in all favorable and

even in doubtful cases. When open reduction is necessary, plastic reconstruction of the acetabulum commonly called the shelf operation gives a high percentage of good results, as shown by the absence of pain or limitation of motion within ordinary ranges, and the ability to engage in milder forms of athletics.[114] There are usually a slight limp and a variable amount of shortening. If the structures surrounding the hip are so short that the head is placed in the acetabulum with difficulty or under tension the final results are not good.

Acute purulent infection of the hip joint may follow or complicate a pyogenic process elsewhere in the body, such as otitis media.[115] In addition to the usual signs and symptoms of sepsis, the thigh is flexed, abducted, externally rotated, and all motions are restricted by muscle spasm. There is usually a tender mass, which may be fluctuant, below Poupart's ligament, and the inguinal glands may be palpable and tender. If there is fullness above Poupart's ligament, it may indicate a pelvic extension of the process from the joint. Every means should be employed to improve the general condition and more than one incision may be necessary for adequate drainage. If the arthritis has been of long duration, osteomyelitis of the ilium may occur with the formation of an involucrum so large that it may displace the bladder, or there may be actual perforation by the sharp point of a sequestrum.[116] In any case of osteomyelitis of the ilium, especially if there is pyuria, a cystogram should be made. The shadow of the involucrum may be obscured or confused in the usual roentgenogram by the shadows of the pelvic bones, but the cystogram will show a marked displacement or distortion of the bladder. Even though there is no pyuria in cases showing such displacement, the possibility of perforation should be considered; the involucrum should be opened, the sequestrum removed, and the osteomyelitic lesion drained through an extraperitoneal incision above the pubis. This will prevent perforation, clear up the osteomyelitis and improve the general condition of the child more rapidly than if drainage is done by the usual route over the joint or through the adductor region.

The treatment of tuberculosis of the spine by operative fusion is superior in the final analysis to the nonoperative treatment since cure depends upon ankylosis, and ankylosis cannot take place in the presence of constant motion.[117] Plaster jackets and braces cannot be effective on account of the uncontrollable mechanical influences of respiration and muscle spasm, and exacerbations or progress of the disease are almost certain to occur. Another adverse effect of nonoperative treatment is interference with respiration which prevents proper oxygenation of the blood and tends to lower resistance. Operation in early childhood is apparently not contraindicated, an adequate preoperative period of rest on a frame or in a plaster shell of some two to three years being the controlling factor in determining the time for operation. During the preoperative period the general condition should be brought to the best possible state by thorough antituberculosis measures. The actual technic of the fusion varies with different surgeons, some preferring the Hibbs method supported by an osteoperiosteal graft,[118] and others relying upon a short rigid graft fusing the fewest possible number of vertebrae and allowing the development of compensatory curves above and below the fused area.[119] The length of treatment by operative methods is not materially less

than by nonoperative ones as prolonged postoperative rest is essential for cure, but the permanence of results is much more secure and satisfactory.

There is a marked tendency to recurrence in a certain type of clubfoot. In this type the heel is often represented by a dimple rather than a prominence, and there is such an imbalance of muscle groups that normal development is impossible, and the forces of growth are constantly working against the corrective measures.[120] Relapses will occur in spite of good early correction, and later operation will become necessary. This is the type in which muscular growth of the lower leg is much slower than normal and in which prolonged cast treatment usually causes bone atrophy. In the more usual type there are three problems, adduction, inversion, and equinus, each of which should be treated in turn beginning with the adduction.[121] Gentle correction by means of casts and wedging, with frequent changes, produces excellent results in about 90 per cent of these cases. Forcible manipulation under anesthetic causes damage which tends to produce rigidity, and a rigid foot in partial correction is less serviceable than a completely untreated one. In the milder type or in cases seen very early, the method of treatment by elastic traction is often effective.[122] This consists of the use of a sole plate with a projection at the outer side from which an elastic band passes upward to be attached above the knee. Traction is maintained continuously and causes rapid correction and overcorrection. After full correction is obtained, the traction may be discontinued during the day in children who are walking; later a plaster night boot should be prepared and its use continued for several years.

One of the effects of lumbar sympathectomy is to increase the circulation to the legs. This has been found useful in relieving the cold, blue extremities of poliomyelitis. A study has been made to determine whether it will not also cause an increase in the rate of growth of the bones of such legs and thus make the difference in length between the sound and the affected side less noticeable.[123] Varying degrees of improvement occurred: in some the rate of shortening was diminished; in others the rate of growth was normal so that there was no change in the relative length of the two legs; and in a few the growth was more rapid than on the opposite side so that the difference in length was diminished. In one group the shortening progressed in spite of the operation. The factors favorable to good results were considered to be paralysis limited to one lower extremity, a mild or moderate degree of involvement, and operation at the age of six or eight years during the period of rapid growth. Growth depends upon normal muscular activity as well as circulation, and in extreme paralysis there is not enough such activity to permit growth even though the circulation is increased by sympathectomy. Since muscles partially paralyzed respond better when thoroughly warm, whether the heat is applied externally or internally, it would be interesting to compare the effect of external heat and muscle reeducation on a similar series of cases. Comparisons, however, are particularly difficult in this disease because of the variation in severity in different localities and different epidemics, the lack of standards for accurate measurement, the marked influence of psychic factors and the variations in personality and methods of different physiotherapists. With such a diversity of fac-

tors influencing the choice of patients and the evaluation of end-results, it is possible to say only that sympathectomy has apparently been a stimulus to growth in some cases, that in others it has done no harm, and that it is impossible to predict for the individual case whether or not it will be of value.

Slipping patella is a condition in which the patella dislocates to the outer side when the knee is flexed. It may cause definite disability. Congenital dislocation or displacement of the patella also occurs and is a somewhat similar condition. There is usually a tight adhesion or band connecting the patella with the intermuscular septum of the external hamstring or with the fascia lata, or both. Operative correction is usually quite satisfactory.[124]

The fate of the average spastic child is deplorable. He is usually dismissed by the examining physician with the statement that this is another case of Little's disease, that very little can be done aside from ordinary care, that he may live a long time or be carried off by some intercurrent disease, and that it would probably be well to send him to an institution. Because the child cannot express himself easily or cannot control the flow of saliva, a diagnosis of mental defect is made, and he is condemned to association with mental defectives or is given about the same intellectual training that is bestowed upon an animal. The parents wander from one medical consultant to another and finally in desperation try anything that attracts easy money by rosy promises. One of the main reasons for the shunning of the spastic child by so many of the members of our profession is that proper treatment calls for so comprehensive a knowledge in such varied fields of medicine and surgery that no one mind is capable of encompassing it all,[125] and the failure to obtain good results is often due to one-sided treatment. There should be a well-rounded team in charge of all such cases, including the orthopedic surgeon, neurosurgeon, medical consultant, dentist, psychologist, and physiotherapist. Endocrine dysfunction and foci of infection require attention; nutrition is partially dependent upon good teeth; knowledge of the intelligence quotient and mental capacity will influence the amount and type of exercise to be recommended; intracranial adhesions or a cyst may require surgery. Only after a thorough study of the individual case is rational and well-planned treatment possible. When normal or fair intelligence is present, physiotherapy and muscle training teach relaxation and control; speech training is necessary in some 15 per cent of cases; occupational therapy is valuable; rest periods or stretching in plaster casts or molds, tenotomies, tenoplasties, and joint stabilization are to be used when indicated. Operations on nerves are of limited usefulness, sympathectomy is unsatisfactory, and transplantation of spastic muscles is disappointing. There are of course occasional cases where there is so great a degree of intracranial damage that little hope can be held out, but the great majority of these unfortunate children can be markedly benefited, and no one should be denied a most thorough examination and careful estimation of the possibilities of improvement. Many of these children have normal or even brilliant minds and what could be more cruel than to condemn casually such an intellect to constant misunderstanding and association with mental defectives?

GENITOURINARY TRACT

Persistent pyuria is the most constant symptom in anomalies of the upper urinary tract and is an indication for a thorough urologic study in any child who does not respond to medical treatment within four weeks.[126] If operation is too long delayed nephrectomy may be necessary when earlier diagnosis might have resulted in saving a functioning portion of the kidney. The prognosis of polycystic kidney is poor, and, in general, it may be said that the less surgery performed the longer the patient will live. A solitary renal cyst may be excised unless it involves the entire organ thus placing it in the class of large fluid tumors of the kidney which should be treated by initial drainage with secondary nephrectomy. An ectopic kidney held down in the pelvis by an anomalous blood vessel must be removed. Incontinence may be due to an ectopic ureteral opening below the vesical sphincter, the ureter being an accessory one and usually draining the upper portion of the kidney. When this portion of the kidney is infected, it may be resected. A ureter ending blindly may give rise to a large abdominal tumor, the correct diagnosis being difficult and being usually made after the abdomen is opened. Strictures, congenital kinks, and aberrant blood vessels occasionally occur and can be relieved by appropriate surgical treatment.

Perinephric abscess causes pain, fever, leucocytosis, and tenderness in the costoiliac region. History of a previous pyogenic process elsewhere in the body is suggestive, and the roentgenogram usually shows a deviation of the spine away from the affected side, elevation of the diaphragm, and the shadow of a mass. There is, however, no definite, pathognomonic sign; abscesses have been found which failed to show typical signs, and abscesses have not been found when supposedly typical signs were present.[127] A fourteen-year-old patient had osteomyelitis of the twelfth rib; a thirteen-year-old one had an infected, ruptured hydronephrosis; and a six-year-old child operated upon after study and repeated consultation showed no local pathologic process.

Tuberculosis of the kidney is not uncommonly associated with surgical tuberculosis elsewhere in the body.[128] The onset is insidious and usually painless, the first sign often being a slight intermittent hematuria. After a variable period frequency and pyuria appear, with perhaps slight loss of weight and gradual impairment of health. The frequency is more noticeable during the day. Incontinence indicates a progressive involvement of the bladder. The diagnosis is confirmed by careful urologic examination and the finding of tubercle bacilli. The condition is often bilateral and always serious, but in suitable cases nephrectomy is advisable and gives good results.

Wilms' tumor is the most common malignant growth in childhood.[129] The onset is painless, and the first sign is usually enlargement of the abdomen by a mass which is firm and not tender. There is usually a mild degree of anemia, but the urinalysis is often normal. By excretory urography the ureter is seen displaced toward the midline, and there is deformity of the kidney pelvis. These tumors are very susceptible to roentgenotherapy, radiation causing a marked and rapid reduction in size. Nephrectomy should be performed during the period of recession as there is always a secondary increase in growth. Two or three postoperative series of radiation should be given at intervals of one month, but recurrence is the rule. An occa-

sional cure is reported, however, and every possible means of eradication should be employed.

About 60 per cent of all valvular obstructions in the posterior urethra or neck of the bladder occur in infants and children under the age of ten years. Such children are usually anemic and undernourished, and give a history of gastrointestinal upsets, dribbling, enuresis, straining on urination, and pyuria.[130, 131] Diagnosis is made by a thorough urologic study. Careful preliminary treatment is necessary, and operation is contraindicated until the general health is excellent and the local condition has been improved as much as possible; flushings, urinary antiseptics, and continuous drainage by indwelling catheter often being necessary. Transurethral operation, using the cautery punch and small instruments adapted to the size of the child, is most satisfactory, and recovery with complete restoration of health is often spectacular.

Infection of the urinary tract by colon bacilli is frequently resistant to the usual urinary antiseptics. Clinical investigation of the use of mandelic acid for this purpose is showing encouraging results.[132] A girl, aged three years, who had urinary stasis with pyelitis, megaloureters, hydronephrosis on one side, uretheral stenosis on the other and a heavy infection with colon bacilli, showed little improvement under treatment by ketogenic diet, methenamine, and ammonium chloride. The urine became completely sterile following the maintenance of a concentration varying between 0.25 and 0.43 per cent of mandelic acid in the twenty-four-hour specimen over a period of ten days. The treatment must be carried out with close attention to detail, it being essential that a high degree of acidity of the urine be maintained and that the fluid intake be not greater than 1,200 c.c. daily. A few patients have had nausea, vomiting, and diarrhea, but under close observation and careful management a high percentage of excellent results have been obtained.

Diverticula of the urethra are rare. A case is reported in a six-month-old infant in whom suppression of the urine was caused by the pressure of the infected diverticulum on the urethra.[133] There was a history of dysuria and dribbling with sudden onset of septic symptoms when the diverticulum became infected, and a tender, rounded, bulging mass in the course of the urethra at the base of the penis, which could be emptied by pressure. Before infection it was not tender. Suprapubic cystotomy was necessary for temporary drainage and diversion of urine while the local condition was being improved, the diverticulum removed, and the urethra repaired. Roentgenography following the injection of an opaque medium is suggested as a diagnostic measure, and removal of the diverticulum before infection has occurred is recommended.

Extensive study and clinical observation have demonstrated that spermatogenesis is absent or at best abnormal in the undescended testis. In experimental animals it has been found to return to normal after the testis is placed in the scrotum, variation in local temperature being a determining factor. Clinical observation suggests that after orchidopexy the human testis becomes fertile, but not to a normal degree,[134] and the obvious difficulty of accurate statistics in unilateral orchidopexy is pointed out. The presence of the testis in the scrotum is not alone an index of fertility, and a clinical study has been made in a series of 336 cases after standards of fertility were established

by carefully controlled estimations in normal individuals.[135] Fertility was definitely proved to be far below normal in a high percentage of all cryptorchids, being rated at 10 per cent before orchidopexy. After orchidopexy 82 per cent of individuals were determined to be fertile.

In the hormone treatment of undescended testis there is some tendency to confusion in the standardization of dosage between the gonadotropic pituitary extract and that obtained from pregnancy urine. Both appear to be equally effective in suitable cases, but the former is administered in doses containing 10 rat units[136] as contrasted to the latter which is recommended in doses of 250 to 1,000 rat units.[137, 138] This treatment should be used near the age of puberty, as excessive development and precocious sexual activity may result in younger children from frequent or large doses. The testes increase to the size which is normal for the age, but the increase of the genitals is greater. The diversity of detail in the many reports on the hormone treatment of undescended testis indicates clearly that, since the last word has not yet been said, a clear, accurate statement of indications and technic cannot be made. In general, it is agreed that this form of treatment has distinct value in most cases where there is not a physical impediment to descent; that it is indicated in those cases which show an associated endocrine dysfunction as with Fröhlich's syndrome; that it is not indicated in young children; and that after the age of eleven or twelve years it should be pushed vigorously using frequent and large doses for nine to twelve months before deciding upon surgical treatment. It may be necessary to discontinue treatment for a period of three months after a course of six to nine months to avoid a loss of sensitivity to the stimulus and possibly to prevent gonadic atrophy which has been observed in experimental animals after prolonged treatment. In some instances orchidopexy has seemed indicated after the testis has descended in response to the hormone treatment to prevent a secondary retraction when treatment is discontinued. There is usually a distinct improvement in the general condition with decrease of weight when there has been obesity, increase when there has been underweight, and improved mental reaction; the latter, however, may well be entirely psychologic in older patients.

When surgery is necessary, the Torek technic is generally considered best for the great majority of cases. The transplantation operation, however, has been advocated,[139] the contention being that the scrotal septum exercises elastic traction. In this operation the testicle is passed through an opening in the septum and fixed by suturing the tunica albuginea to that of the normal testis, thus placing both testes in one side of the scrotum. When the Bevan operation is chosen, it is particularly necessary to cut the lower margin of the internal ring and separate very thoroughly the fibers, which will be found just within the abdomen beneath the peritoneum attached to the cord, preventing the descent of the testis.[140]

The question of malignancy in the undescended testis has been thoroughly discussed at great length. A particularly careful and unbiased analysis of approximately 40,000 hospital admissions of male patients shows that tumors of the testis occur twenty times as frequently in undescended as in normally located testes.[141] Two per cent of patients with undescended testes developed testicular tumors, and only 0.01 per cent of testicular tumors occurred in persons with normally descended testes. Other factors are concerned, however, and it was

not determined whether all undescended testes are potentially malignant or whether the factor of nondescent is the determining factor in the development of malignancy.

The treatment of hypospadias requires many operative stages, and it is well to be certain that the parents of a child so afflicted understand this fact distinctly. If there is contraction of the ventral side of the penis, this deformity should be corrected before the age of two years after which three or four years should be allowed for development of the parts before plastic reconstruction of the urethra is begun.[142, 143] Several methods are available, and the choice for the individual case will depend upon the type and degree of the defect and the experience of the surgeon. The technic is difficult and requires special skill and careful observation of the principles of plastic surgery, but reasonably satisfactory results can be obtained. To be classed as satisfactory, the urethra should be of full length and adequate caliber, and the meatus should be at or near the normal position of the frenum. The attempt to bring the urethra through the glans so that the meatus shall be in the normal position involves the danger of hemorrhage and hence is inadvisable in most instances. The parents are usually concerned regarding ultimate function, and they may be assured that with the physical result mentioned function will be normal.

Cysts or canals of the genitoperineal raphe may be found in young children.[144] They occur at any point along the midline of the perineum, scrotum, or ventral surface of the penis and are usually symptomless unless infected. They are lined with dermoid or mucous cells, depending upon their origin. They do not communicate with the urethra and hence do not cause pyuria even when infected, but they sometimes cause pressure upon the urethra. If infected, they should be laid open widely; but, if uninfected or if the infection is subsiding or chronic, excision is advisable and is followed by rapid healing.

Malignant tumors other than those of the kidney are rare in infancy. Myosarcoma of the prostate in an infant eight months old caused suddenly developing suppression of urine with pain, straining, and edema of the perineum.[145] The rapidly growing mass caused death in about three weeks in spite of suprapubic and perineal incisions. Carcinoma of the uterus in an infant fourteen months of age caused vaginal bleeding, discharge of varying amount and foul odor, and a palpable mass on rectal examination.[146] Deep roentgenotherapy was of little effect, and after one year metastases and a rapid increase in growth took place with death at the age of thirty-two months. The possibility of hysterectomy was not mentioned.

The sex-linked characteristic of hemophilia has stimulated study of the treatment of this condition with female sex hormones and placental extracts.[147, 148] Theelin has been found to be the most potent ovarian extract. The oil solution is the preparation of choice, as the aqueous solution has little effect. It is available in 1 c.c. ampules containing 1,000 international units each. Marked improvement or complete control of bleeding in hemophiliacs and nonhemophiliacs usually follows the injection of one ampule every two hours for three or four doses. If the condition is urgent, two ampules may be given at the first dose. Severe stinging pains at the site of the injection may be prevented by drawing 4 or 5 drops of novocaine into the syringe after the theelin, injecting it first, and waiting some thirty

seconds before injecting the theelin. A blood coagulant extract of human placenta has proved effective in eleven of fifteen cases of hemophilia.[148] Oral administration is effective in fifteen or twenty minutes, whereas the effect of intramuscular injection may not be apparent for several hours. Extreme care is necessary to avoid entering a vein as this has proved fatal in experimental animals. The good effect remains for two to nine days, and the treatment may be repeated, children having been able to live normal, active lives for a period of several months under the continued administration of this material.

The treatment of hemangiomas depends upon the size and type of the growth.[149] An experience extending over four and one-half years and including 697 cases indicates that 80 per cent of port-wine marks are cured or markedly improved by treatment with the Kromayer light; over 50 per cent of the spongy, capillary type are cured by carbon-dioxide snow; and endothermy under anesthesia is effective in the large, lobulated ones or those having raised purplish bases. Excision is advisable when the location and size are favorable. The results from treatment by radiation and fulguration have not been as satisfactory as by these other methods, as the sequel is often rather marked scarring. The treatment by the Kromayer light and carbon-dioxide snow requires many stages over a long period of time but usually results in a skin slightly smoother than normal without scar contraction.

TREATMENT

In determining the prognosis and treatment of many conditions, the blood sedimentation rate is of great value and should be more generally used.[150] The cause of this reaction has not been definitely determined, but sufficiently extensive observations have been made to bring out a number of facts regarding it. The test should be done with exactness and interpreted with the knowledge that minor variations are usual and are not significant. In the newborn, sedimentation is normally slow, but for children and adolescents the normal values are the same as for adults. Changes in the sedimentation rate occur more slowly than changes in the leucocyte count and temperature, and the return to normal is slower. Complications developing in the course of an acute infection cause a rapid increase in the sedimentation rate. In simple catarrhal inflammation or in the early stages of acute inflammation of the appendix, it is normal. In joint tuberculosis it is increased, providing a valuable differential point between this condition and Kohler's or Legg-Perthes' disease. It is especially useful in indicating the presence of occult organic disease and in estimating the progress of chronic infections, such as tuberculosis or rheumatic fever. Its value is increased when it is used in conjunction with the Schilling blood count, and these two tests should be considered as supplementary. A series of tests is better than isolated ones.

In the treatment of chronic staphylococcic infections of the skin, staphylococcus toxoid has given good results.[151] It is recommended in gradually increasing weekly doses beginning with 0.05 c.c., controlling the dose by the patient's response and general condition. The toxoid gradually deteriorates and will lose 40 per cent of its antigenic power in six months even when kept in the ice box.

A study of the treatment of wounds by hypertonic solutions of sodium chloride or magnesium sulphate applied as wet dressings in-

dicates that they are of little value.[152] With the lower concentrations the layers of gauze in contact with the wound soon become isotonic, and even with high concentrations the strength of the solution in the innermost layers is markedly reduced. The amount of water which can be withdrawn from a fresh wound is 1.2 to 1.5 c.c. per square inch of surface per hour, regardless of the degree of hypertonicity, and with granulating surfaces there is great variation. As water leaves the tissues, the concentration of serum becomes greater, and there is soon a return flow of a weak solution of salts, according to the laws of osmosis, and the tissues become boggy and edematous. The effect on phagocytosis could not be determined, but the action of the hypertonic solution does not extend into the deeper tissues where active infection is often located.

Contused, lacerated wounds, and recent burns which are contaminated may be treated effectively by cod liver oil dressings.[153] Gauze saturated with oil is applied directly to the wound and on a burn where a minimum of manipulation is desirable it may be applied without preliminary removal of the greasy detritus which is often the result of first-aid treatment. At the end of twenty-four hours the superficial dressings are removed, and the lower layers of gauze are resaturated with oil. Changing of dressings once in forty-eight hours is usually sufficient. Cod liver oil is bacteriostatic and stimulates the formation of healthy granulations. Epithelialization proceeds rapidly with formation of a smooth scar without pigmentation even in third-degree burns. Granulations may become exuberant at the end of a week, and some other type of dressing may become necessary to inhibit them. It seems possible that the action of cod liver oil may be similar to that of peptone broth in stimulating activity of the reticuloendothelial system.

Of especial value in children is the novocaine pack as applied to minor wounds requiring suture.[154] After oozing has been controlled by pressure or adrenalin, gauze soaked in novocaine is applied directly to the wound. Any available solution from 1 to 5 per cent may be used, effective anesthesia for a distance of nearly 1 cm. from the edges of the wound being obtained in from five to eight minutes, depending upon the strength of the solution. It may be used before cleansing, making that procedure less painful, and since distortion of the tissues by infiltration is avoided it is possible to obtain better cosmetic results.

The treatment of surgical shock is directed primarily toward the restoration and maintenance of blood volume which is accomplished satisfactorily in most instances by the intravenous administration of saline and dextrose solutions.[155] Blood transfusions and the use of acacia solutions are of great value, but caution is necessary in the case of the latter that it be not used in too large amounts. The use of sodium bicarbonate solutions intravenously is not advisable, but 10 per cent alcohol in a solution of 10 per cent dextrose is recommended. The administration of alcohol in this manner is rather unusual, and it is doubtful whether it possesses any advantage over dextrose combined with insulin, as whatever value it may have is no doubt due to its being a quickly available, diffusible carbohydrate.

In surgical shock, fluid does not usually leave the body, and the problem consists in returning it to circulation. In dehydration from other causes, however, it is often necessary to supply salts as well as fluid. This is particularly true in children, in whom the necessity of fluid for the maintenance of normal function is even greater than in

adults. The loss of fluid from discharging wounds and vomiting should be estimated and careful attention paid to blood concentration and urinary output when there is the least possibility of dehydration. A loss of fluid amounting to 6 per cent of the body weight produces a serious dehydration and is often accompanied by albumin, blood, and casts in the urine, indicating that there is insufficient fluid to maintain normal kidney function.[156] In the presence of these signs water must be supplied in plentiful amounts in as short a time as possible. If vomiting has been a factor in the dehydration, sodium chloride should be supplied until the blood chemistry is normal but not in greater amounts on account of the danger of causing edema. If more fluid is necessary, glucose solution may be used as the glucose will be oxidized leaving the water to supply the body tissues. The necessary amount can be determined by the urinary output, as the kidney excretes only what is left after the tissue requirements are satisfied, a daily excretion of about 1,500 c.c. being a reasonable standard. When the necessity for fluid is acute, 5 per cent glucose in saline intravenously is widely used.[157] Ten per cent glucose in saline is used to supply carbohydrate and for the treatment of acidosis or insulin shock. Dextrose in Ringer's solution or Hartmann's solution is used when other salts are needed. Opinions regarding the speed of large volume injections vary, 500 c.c. per hour being an average rate for adults. A safe rule is that dextrose solutions should not be injected at a more rapid rate than ⅓ gm. per hour per pound of body weight. Hypertonic solutions should be given more slowly than isotonic ones. In shock, fluids may be injected at the rate of 20 to 40 c.c. per minute until the pulse reacts, then more slowly. The temperature of the solution is not important when it is given slowly.

Fluids may be given by continuous intravenous infusion for periods of several days, but this method should be used only with judgment and under careful observation as it is not without danger.[158] There should be no cessation of flow through the needle since this favors backflow of blood and clot formation. General edema or edema of the lungs may occur from an overburdened circulation or improper proportion of salts. Kidney irritation as indicated by hematuria may follow a too prolonged intravenous administration of 5 or 10 per cent glucose, and embolism has been reported. In general, it is better to use intermittent rather than continuous intravenous infusion, the indication for the latter usually being a paucity of suitable veins and the probability that the treatment will be required for a long period.

The value of blood transfusions is unquestioned, particularly in the treatment of shock and hemorrhage, and transfusion may be used to good advantage in many of the infectious and nutritional disturbances in children. The indirect gravity citrate method is perhaps the most suitable for general use as it is less expensive and requires less apparatus and less teamwork.[159] Cross-matching should be done even though donor and recipient are in the same group, as occasionally there is incompatibility due to difference in subgroups. Even with this precaution, nonspecific reactions may occur consisting of rise of temperature from 0.5 to 2 degrees and lasting from a few minutes to an hour. In a series of 207 transfusions such reactions seemed to be beneficial rather than otherwise, and there were no hemolytic reactions. The blood must be kept warm; special care is recommended in preparing and cleansing the apparatus. At variance with the experience in this series in which the value of transfusions in septicemia is

questioned is a report that multiple small transfusions every forty-eight hours until the blood culture is negative produce excellent results in septicemia.[160] Transfusions should be begun early before resistance has broken down and metastatic lesions have developed. Immunotransfusions are best. Septicemia, particularly that due to the staphylococcus, is always a serious condition, and the factors influencing individual resistance are so diverse that differences of opinion based on different series of cases are inevitable. Any method of treatment which has produced good results should be reported so that it may be available to others in case of need.

Interesting observations have been made in Russia upon the use of cadaver blood for transfusions.[161] The blood is obtained from persons dying from accidents and may be preserved in the ice box for a period of four weeks. Such blood does not clot and hence does not require citration. There is ample time for Wassermann tests and tests for sterility, and the therapeutic effects are the same as when blood from living donors is used. It may be possible that if regimentation becomes more general in this country or perhaps in cases of extreme emergency cadaver blood will be used, but for the present a certain psychic factor will probably limit the popularity of this procedure.

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American Academy of Pediatrics

Proceedings

SIXTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

KANSAS CITY, MO., MAY 11 AND 12, 1936

Round Table Discussion on Childhood Psychiatry

Chairman: Dr. Franklin G. Ebaugh, Denver, Colo.

Assistants: Dr. Leo Kanner, Baltimore, Md., and Dr. James S. Plant, Newark, N. J.

CHAIRMAN EBAUGH.—I want (1) to present briefly the psychobiologic point of view as applied to the handling of children's problems, (2) to outline what is now being done by the departments of pediatrics and psychiatry to prepare students to deal with the behavior problems of children, and (3) to offer some suggestions as to the fundamentals of a psychiatric training program.

Everyone accepts the pediatrician as the general practitioner of childhood. Pediatrics has been defined by Veeder as "that branch of the medical sciences which has to do with factors influencing the growth and development of individuals from birth to maturity," but pediatricians have, in the past, limited their attention principally to the child's physical development—to heart, lungs, kidneys, weight, and body fluids—and have ignored the interesting problems of the child as a behaving or misbehaving personality. They have avoided, in teaching schedules and in clinical practice, the emotional and personality problems of childhood. Yet we all agree that this phase of modern pediatrics is now assuming great significance, since educators, psychologists, and psychiatrists have been accused of taking it over. Furthermore, parents who have always taken their children to the pediatrician for physical care frequently decide to go elsewhere with problems relating to behavior.

The pediatrician has several methods of dealing with this situation: he may be on the defensive, scoff at and belittle the achievements in the field of behavior studies, or he may decide to meet his difficult situation by acquiring an understanding of the principles that underlie the development of the personality, its emotional disorders and their adequate management. But the physician who adopts the second course is often bewildered and antagonized by what Dr. Brennemann has aptly designated as a "confusion of theory and authority." Wishing to enter the field of behavior study, he notices that there are many psychologic schools, each with biased emphasis on one factor or another. He does not know which way to turn and usually loses his interest in a feeling of resignation, deciding to get along as best he can without psychiatric assistance.

For these physicians, who are lost in a confusion of doctrines of focal infection, endocrinology, theoretical brain localization, behaviorism, or the cultural-mythological theories of the various psychoanalytic schools, it seems to me that the present-day emphasis on the psychobiologic point of view in dealing with problems of behavior offers a practical solution. The psychobiologic point of view avoids one-sided ap-

proaches and offers no ready-made formulas that can be immediately applied to all children. It deals with demonstrable actualities rather than hypothetical claims and is willing to accept from any worker or any school of thought that which has been satisfactorily proved to be a factual contribution. It adapts its methods to the need of the individual child instead of adapting the child to the rigid postulates of a theory.

In recognizing the importance of psychobiology, I have no intention of belittling the part played by anatomy, histology, or physiology in adding to our understanding of the human organism. What I wish to point out is that they, in themselves, present only single aspects of this highly complex and integrated unit, while psychobiology takes into consideration this unit as a whole, inclusive of all the "ologies." It deals with mentally integrated behavior in its human totality, that totality of the behaving organism to which Meyer refers as "he," "she," "you," or "I"—in other words the individual or person; and it deals with this individual in his relationships to other behaving individuals. We cannot approach, therapeutically, a mysterious brain center, the location or even existence of which is uncertain, but we can work with a child as a person and with his parents or teachers, as well as with the situation to which the child is reacting in the home, the school, and the community. In the mental development of the child, there are critical periods and successive levels of mental integration or personality formation. In the study of the child at any given moment, we are dealing with every experience the child has had previously, in a genetic-dynamic relationship. In the words of Tennyson's Ulysses, it is literally true that "we are a part of all that we have met."

Psychobiologic Methods as Applied to Children's Problems

In the care of the child, how are psychobiologic methods applied? How practicable are these methods for the use of the general practitioner? The psychiatrist has no short cut and but few instruments of precision at his disposal in dealing with behavior problems. From the very nature of the subject matter, the understanding of childhood behavior is a complicated and often laborious business. I do not like the term "psychiatric technic"; I doubt if such a technic actually exists. The child is brought to the physician's attention with a complaint, which varies from an exanthematous condition, otitis media, whooping cough, lesion of the skin, to constant blinking of the eyes. The means of investigative pursuit do not smack of the metaphysical, nor do they imply special procedures known only to a select few. On the contrary, they embrace the common-sense approach which any physician utilizes in sizing up a problem with which he is confronted. The patient's complaint forms a nucleus about which the study proceeds. We overlook a great deal that is important when we do not give the child and the parent an opportunity to talk. Psychiatrists, therefore, pay particular attention to the complaint, and complaints should always be obtained from several sources. This has been especially emphasized in a recent paper by Kanner.

The significance of the data secured by this method can perhaps best be illustrated by a clinical example:

> Complaint from teacher: "John is failing in everything. He can't do mental arithmetic."
>
> Complaint from mother: "John is slow, just like his dad. It must be hereditary."
>
> Complaint from John: "They don't like me in school. I have a hit-and-run teacher. I won't go to school."
>
> The "hit-and-run" teacher, he later explained, before assigning problems in mental arithmetic would point or lunge at him, stating that he was so slow she didn't expect him to answer the problem, and she would never repeat the problem given. John admits that he responded by doing nothing,

although occasionally he spent his time carving initials on the school desk. It is of interest to know that the complete examination in this case indicated that we were dealing with a child of superior intelligence and that the mother of the boy was enmeshed in a most turbulent and unsatisfying marital situation, along with the stress and strain of bringing up a family of four children, of whom John was the youngest and the result of the most undesired pregnancy.

The clinical advantage of the complaint in psychopediatric work is the clue that it gives to the attitude of those dealing with the children—its general educational and self-educational significance to the physician. It lends itself to a systematic grouping of the many items and difficulties commonly met with in psychopediatrics, at the same time serving as an indicator in the reformation or diagnosis and as a check on one's therapeutic success or lack of it.

Having obtained the complaint, we proceed to develop the story, reconstructing the setting in which the difficulty arose, tracing its development from its outset to the present time, and particularly noting its effect upon the individual and his environment. In short, we approach the problem as we would any that challenges us in the scientific world, by ascertaining the conditions under which it develops, the predisposing factors, their work or course, and the results to which they have given rise.

In addition, a personal history is taken, with emphasis on the personality make-up of the child, his characteristic performance, parent-child relationships, school and group behavior, and the like, as well as the physical factors. The family history completes the indirect examination.

The direct examinations of the child consist of the usual routine, complete physical studies including indicated contributory examinations, that is, laboratory, x-ray, etc., mental measurements, and the so-called psychiatric examination, in which special emphasis is placed on the child's emotional life and habits, as well as on the various features of his environment and their possible direct or indirect connection with the difficulty to be treated. Here we are dealing to a large extent with interpersonal relationships between parents, teachers, and the child. The mental health of the child may be determined by his maximum ability to get along with people in a manner that will contribute mutual satisfaction on a constant give-and-take basis, without the interference of inner conflict or external friction. The child is not only a biologic, but also a highly differentiated sociobiologic, unit. A study of the child's environment demands no unusual theoretical preparation, but simply an elaboration of the complaint in the light of the actual manner in which the child gets along at home, in school, and in the community. The physician becomes increasingly aware of certain home situations centering around parent-child relationships and poor personal relations, such as domination by one member of the family, interfering by relatives, favoritism, maladjustment due to the fact that the child was unwanted, clash of authority, dissension between parents either overt or otherwise, oversolicitude, overseverity, neglect, jealousy, difficulties with a step-parent, ineffectuality of parent, important physical and mental disabilities in parents, as well as significant social, economic, and moral maladjustments in the home.

Also contributing are school situations which influence behavior, such as (1) personal relationships based on antagonism between pupil and teacher, conflicts between home and school, and the like; or (2) disabilities of the teacher which influence a child's behavior; such as neuroticism or poor physical health, insecurity, and lack or inadequacy of training. In the same way, a rigidity or poorly organized school curriculum often influences the behavior of the child, as do community situations, especially lack of public interest in school and health problems; inadequate provision of recreational outlets for children; community attitudes toward delin-

quency; isolation of groups differing in language, customs, and race; and congestion of population.

To summarize, therefore, the psychobiologic approach to the study of childhood behavior problems is based on a pluralistic attitude in which we single out some happening or group of happenings, either pathologic or normal, in the transit of a person through life and study it for what it does and is in relation to the whole situation of that individual. In the consideration of a child, we wish to ascertain (1) the conditions that gave rise to the complaint, (2) the predisposing factors, (3) their working or course, (4) their results, and (5) the modifiability of the whole.

In dealing with children, the diagnosis is expressed in terms of the individual problems with which we are confronted. This tells us more than general terms such as "nervousness," "neurosis," "neurasthenia," "behavior disorder," and the like. It is always the child, as a person, that we wish to treat, not merely his tics, enuresis, temper tantrums, or fears, as diseases or symptoms. The therapeutic program depends on the completeness of the direct, indirect, and contributory examinations, with the conclusions we have drawn from them and what we have recognized to be the child's personality assets and liabilities.

Psychiatric treatment is, therefore, the total of efforts made in behalf of the adjustment of an individual with personality difficulties. Its first aim is to set up in the patient a condition of comfort and well-being and, in general, a feeling of security. This means the utilization, by the physician, of a psychotherapeutic approach. Psychotherapy is essential in the therapeutic armamentarium of any physician. I define psychotherapy as "an effort to influence in the right direction the attitude of the patient toward himself, toward his mental and physical processes, toward his environment. It is an effort to teach him to understand himself, his illness, and the cause or causes of his illness, whether this cause or these causes lie in the body, in his environment, or in the superficial or deeper layers of his mental life." Psychotherapy, as it deals with the child, rests on an aeration or ventilation of the conflict material presented by the child, by means of direct interviews in which the child is given an opportunity to discharge and bring out into the open all the life experiences that have been causing him serious concern. Psychotherapy includes also desensitization, whereby the patient is required to face frankly the traumatic experience of the past. Suggestion, persuasion, reassurance, and reeducation are necessary psychotherapeutic adjuncts in dealing with the child. Reeducation especially leads to the establishment of new habits of response and the development of social, recreational, and activity programs to insure future stabilization. In psychotherapy, there is always a need to desensitize the patient's family to his illness and to influence them in new habits of response to the child. This is of great significance in the type of behavior manifestation so often encountered in the "overprotected child," who frequently develops temper tantrums, hypochondriasis, loss of initiative, and continued dependence.

Other types of treatment center around the fundamentals of general medical treatment, especially as it pertains to the physical well-being of the child. Environmental shifts, such as placement of the child in a foster home, may be an essential phase of the treatment occasionally, although as a general principle it is best to further the adjustment of the child directly in the home. For this purpose, the social worker's aid will be more and more solicited and utilized to the fullest extent possible. I need not emphasize the importance, in the social-therapeutic regime, of establishing general recreational facilities in the community.

I have briefly reviewed the psychobiologic viewpoint as applied to children's personality difficulties. I hope that it does not appear mysterious and that the terminology, aside from the use of the word psychobiologic, has not confused you. Because of its emphasis upon the person rather than upon the disease, psychobiology

is fundamental for all of us if we accept our full obligations in dealing with the child. In our medical training, we are apt to be preoccupied with organs and systems, or with physiologic segments and part-functions, instead of with the more sweeping and total functionings of the individual, in which he must be viewed, as described by Adolf Meyer, as a mentally integrated behavior. I feel that the pediatrician who is responsible for the care of children should adopt this pluralistic attitude in meeting the interesting problems of childhood, instead of becoming confused by the various schools of thought and involved in controversy among ourselves. Psychiatrist, pediatrician, and general practitioner should adopt a conjunct approach based upon thorough and practical medical training, which should include both undergraduate and postgraduate studies. This seems to me the real solution of what Dr. Brennemann has signated as a "confusion of theory and authority." For practical purposes, it is to be expected and accepted that the pediatrician and the general practitioner dealing with children should assume their shares of responsibility for the personality difficulties of childhood. This means that they should take care of the majority of such problems. The psychiatrist may be utilized, like any other consultant, to deal with the more complex and involved behavior problems. It is anticipated that we will have fewer of these problems if the pediatricians adopt an attitude in dealing with the mental phenomena of childhood similar to the attitude they have so successfully utilized in dealing with the physical care of the child. It may be accepted that psychiatry must assume the responsibility for court work and many other special phases pertaining to childhood delinquency and the relation of these problems to future mental conditions, especially the minor psychoses (the psychoneuroses) and the more sweeping mental reactions of the adult.

Present Status of Training in Child Psychiatry in Relation to Pediatrics

A review of a recent study of the situation in our medical schools is most pertinent to our discussion. The teaching content of the departments of pediatrics during the current year indicated that only brief formal instruction in the field of child psychiatry and mental hygiene was given in fourteen of the sixty-eight four-year medical schools visited. In the remaining schools many professors of pediatrics volunteered the information that no attempt was being made to present the psychiatric viewpoint throughout the instruction in pediatrics, or that, owing to lack of time, there was a complete omission of teaching in this field. In fact, at the time of this study, only four schools gave evidence of formal organization for such teaching within the department of pediatrics, although several other schools had made arrangements for staff participation in seminars or an occasional lecture in child psychiatry and mental hygiene. Liaison work between the departments of psychiatry and pediatrics, in some degree or other, existed in nine schools. Opportunities for such elective work in pediatrics were also meager. Child guidance facilities of some kind were available in twenty of the schools visited. In several localities adequate child guidance clinics were available but were not utilized in the teaching schedule, because of isolation, lack of interest on the part of the university departments, or lack of desire to participate in teaching on the part of the director of the clinic. It was most striking to note this lack of utilization for pediatric teaching of the facilities available. In the schools that have a psychopathic hospital or institute, facilities for child psychiatry have usually been established as a part of the regular out-patient activities and more extensive individual instruction is given, frequently at the request of the pediatric department. However, these facilities are not utilized in the general interne training. The outstanding work at Cornell University Medical School under Dr. La Mar, at Johns Hopkins University School of Medicine under Dr. Kanner, at Washington University Medical School under Dr. Kubitschek is well known to you.

The groundwork, therefore, for the complete care of the child, utilizing the experience of both fields, has been established and much good work is now being done which promises further progress in the near future. This again will lead back to the objectives of the general medical curriculum. If we accept psychiatry as that phase of medicine which deals with the pathology and therapy of the person, we must aim to produce a practitioner who, on graduation from a Class A medical school, has acquired a sound attitude toward professional duties and responsibilities and an ability to deal reasonably well in the early days of practice with the rank and file of patients and conditions that will confront him. The medical curriculum, likewise, throughout each year in the medical course should be directed primarily toward health, its preservation, perfection, or restoration, and not toward disease. From this point of view, we are compelled to accept a psychobiologic approach to problems of health and disease, in that we are always dealing with a person and not a walking test tube containing some fascinating disease process. Likewise, the medical curriculum should not continue to be divided into separate blocks of study, but all departments should be to some extent interdependent. In this connection, I believe again that psychobiology is an excellent connecting link, correlating the preliminary medical sciences with the clinical sciences. It is to be anticipated that the medical curriculum of the future will not prescribe or standardize any strict uniformity of method in the teaching schedule. There will be a wide liberty of choice in the different schools, each of which should provide broad general foundations and requirements for the basic medical training. When the general practitioner and the pediatrician get their grounding in psychiatry in the medical school, "the confusion of theory and authority" will no longer exist. If this comes about in the undergraduate teaching schedule, we may anticipate a similar development in the field of graduate education, with specialization based on thorough experience and fundamental training as elected by the individual physician.

Fundamentals of a Psychiatric Training Program for Pediatricians

I have often been asked the difficult question: What constitutes the irreducible minimum in the way of a foundation for the orientation of the general medical man or the pediatrician who assumes responsibility for the emotional and personality problems common in childhood? It would be impossible to formulate such minimum instructions. Too much depends upon the individual who is doing the teaching, the content of the course, and the special interest and initiative of the person receiving instruction. Such instruction should be very flexible, but I would consider the following as fundamental:

The physician or pediatrician should know how to administer the Binet-Simon test and be sufficiently aware of its limitations to interpret it wisely. He should develop insight into the individual aspect of behavior problems. When intensive individual study is required, the case may be one appropriate for psychiatric consultation, but the pediatrician must be capable of caring for the less complex cases and of appreciating the length of time necessary in psychiatric study, where formulas of "do this" and "don't do that" are of no value. The pediatrician who desires such training should spend at least one year in preparation (preferably two), having contact with the important phases of social and clinical psychiatry. Special elastic training programs and requirements should be established in various centers to meet these needs and to give the pediatrician some understanding of such fundamentals as these:

Mental growth and development of the child.

Behavior as an interaction between the child and his environment (motivation of behavior, symptomatic and genetic-dynamic aspects).

Common home, school, and community situations that influence child behavior.

Factors that enter into the development and training of habits (eating, sleeping, elimination, sex, etc.).

Etiologic classification of the common behavior problems of childhood.

Methods of behavior study (social, physical, psychometric, psychiatric).

Methods of management and treatment (direct, indirect, social-manipulative, psychotherapeutic; in general, clarification and interpretation in contrast to direct corrective measures).

Origin, development, aims, and application of mental hygiene.

Individual discussions concerning the hospital care of behavior disorders and borderline states in childhood indicate clearly that the consensus of opinion in both the pediatric and the psychiatric groups is that these problems should be handled in a children's hospital and that adequate facilities should be developed there. This certainly is preferable to the tendency in some psychiatric hospitals to add wards for children and consider these problems in relation to the major adult problems.

Conclusion

In conclusion, I should like to reemphasize the following points:

First, psychiatry in the care of a child has a clear-cut contribution to make to general medicine and pediatrics in its psychobiological attitude; that is, the attitude that deals with the total child by the general principles of clinical history and examination, with special emphasis on the complaint factor. Psychobiology gives us a pluralistic attitude toward behavior problems and is based on demonstrable facts and not on any theory or system or special school of psychology.

Second, it is evident that the general practitioner and pediatrician must stand as the first line of defense in dealing with the personality and emotional problems of childhood and that, in actual practice, the responsibility will fall on them for handling such problems in their incipiency.

Third, medical education and practice cannot be separated. We, therefore, should bring about throughout the whole medical curriculum greater correlation between the preclinical and the clinical sciences, along with psychobiologic concepts, emphasis upon prevention, and greater recognition of medicine as a social agency. Interdepartmental and liaison activities between the departments of medicine, pediatrics, and psychiatry are now demonstrating the practical applicability of a conjoint approach to personality problems in childhood which promises much for future clinical and therapeutic endeavors, as well as for the training of a personnel in the field of general medicine and pediatrics that will be competent to deal with the rank and file of childhood behavior manifestations.

But either way it goes, it's interesting. Either way it goes, it leads us to fields of adjustment that are richly carpeted with strange and exciting flowers. Either way it goes, we meet sickness and health just as truly as in the matters of organ function.

For many of you—as for many psychiatrists—I have said nothing that is new. For the rest, psychiatrists as well as pediatricians, if you care for rare adventure, if you can stand failure and foolish error, if you don't become too disturbed over exotic theories and practices that burst into flower overnight in a new field—you will enjoy practice in a community more than you ever enjoyed practice in a person.

The Practice of Psychiatry in a Community Clinic*

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The position of the psychiatrist in community work is much the same as is that of many of your leading pediatricians. We in psychiatry have just as many in our field who are preoccupied with the symptoms of mental disorder as you have who

*The author apologizes that this material rather closely parallels his longer article, "The Promise of Psychiatry" (Am. J. Dis. Child. 44: 1308, 1932). It is less interesting but a bit more honest to recognize how slowly one develops.

are interested in the diseases of children rather than in children. If you point with some apprehension to the glittering blandishments of psychoanalysis, are you not really equally disturbed by such as your own vitamin "racket"? If you are struggling to adjust yourself to a new level of integration and to questions and problems which have not come to you before, so are we.

In other words, I see pediatrics and psychiatry moving shoulder to shoulder out of the realm of weight charts and hallucinations, out of the realm of disease entities and syndromes, into the field of the adjustment of the individual in a complex world. In the light of these common interests and problems let us review simply what it is which we face.

First, with a marked and rather sudden decrease in the time and energy occupied in the mechanics of living, many bewildered people have turned to bridge, golf, and mad rushing about in speeding automobiles. The significant change, however, has been that of a marked increase in the interest in the relationships of living. The harassed parent of a large family who for centuries has asked "What can I do for others?" is now querying "What do I mean to others?" Problems of food were earlier few because for the busy mother Johnny could jolly well eat his spinach or do without. (Notice that the tasks of life managed to produce something of that same detachment which in various ways we labor for now.) Today the same difficulty principally raises the questions, "What does this *mean?*" "Who's going to win?"—questions which soon completely supersede all problems of the food itself.

Posterity will look upon this rapid shift of interest from the mechanics to the relationships of living as the most dramatic and, in the end, most worthwhile development of our generation. And let us not fool ourselves—psychiatry is little, if any, ahead of pediatrics in meeting the issues that have been raised.

Second, and this is probably rather closely related to the above, there is a widespread and discomfiting question as to *why* things are happening. Parents earlier satisfied if the youngster ceased sucking his thumb now ask why he has been persisting in the habit; families earlier happy over the clearing of a conduct disorder now seem more interested in the reasons for the change than in the change itself.

Here again we progress. "Why" will lead us much farther than "what." But for the present this means serious trouble for both of our groups. We have, to date, moved farther than you in this sector. Psychoanalysis, for all you may wish to say against it, is at least an attempted answer to a question which most of us are only trying to run away from. We shall not still these queries by making fun of them. If you do not like such answers as we have made as to "why" people behave as they do, build some answers of your own; do not just stick your heads in the sand.

Third, while every generation has had to consider itself "critical," has had to feel that its problems surpass those of other times, it seems fair to say that our times have been presented with problems of social adjustment rather more complex and pressing than those of any other time since the Renaissance. Urbanization, staggering problems in facility of communication, and rapidly changing types of machinery have tumbled upon us in dismaying rapidity. And for various reasons a bewildered populace seeks an answer from the physician. The overanxious mother and the questioning young wife are no less "sick" than are those with some organic disturbance. True, the illness is less sure of diagnosis, the "history" lacks clean-cut points, the therapy is a long, hard struggle through a maze quite as baffling to the doctor as to the patient. Are you and I blind that we would try to pretend that these are not real illnesses just because we cannot circumscribe them with our usual diagnostic terminology? Are we quitters, that we would turn away because the problems seem too complex?

Most of my colleagues feel that at this point psychiatry has gone much farther than has pediatrics. With this I personally cannot agree. I feel that the psychia-

trists in general have been quite as blind to the problems raised by the social pressures as have your group been. The psychiatrist is still satisfied to bring the patient for treatment many miles from his accustomed milieu—is still willing to study the lion at the zoo, quite oblivious to the fact that what he sees there is no real lion.

Such are the problems which face us, and, right or wrong, some assay of the effectiveness of our various approaches. Just because I can use social workers I think that certain avenues of information and therapy are open to me—avenues I think you know very little about. Just because I sit in various classrooms or know the recreation leaders or policemen in my area better than I know the parents, I think that I have certain insights into the problems the child has to solve—insights which are beyond the view of the practicing pediatrician. Just because I like to think of myself as a sociologist rather than a psychologist, I think that I came upon my problems with a point of view different from yours. Yet I would have failed utterly today to make myself clear if I gave you any other impression than that the problems and perplexities that are yours are really also mine and are those, too, of my colleagues.

The platform upon which I work is a very simple one. It has only two important planks. One bolsters and patches, repairs, and makes fancy additions, but the practice of pediatrics or psychiatry in the community can comfortably operate on two very homely principles.

The first is to recognize that in every sort of conduct disorder the child is trying to solve a problem. There are times when we adults can see that no problem really exists, but it exists for the child. There are times, aplenty, when we feel that the child's method of solution is faulty. I can assure you, gentlemen, that when a child sucks his thumb, or plays hookey, or springs a temper tantrum, he is trying in his own way to solve what he sees as some sort of a problem, and I can assure you that until we find what problem the child was trying to solve, we can do nothing to help him. Virchow taught us not so long ago that physical disease is nothing but this same effort on the part of the normal body to solve a problem. He revolutionized the practice of medicine. To preoccupy yourselves with the disappearance of lying, truancy, nail biting, or masturbation is about as sensible as to persuade yourself that your pneumonia patient has no fever or your fracture case, no pain.

The second is to rigidly follow the rules of Dr. Anna Freud as to the practice of psychiatry in children. There are three of these rules. They come from an analyst, but they are good ones. They will carry you farther than all the trick technics of a technic-crazy culture.

The first is easy. Have unending patience.

The second is hard. Have faith in the child. With most of the enuritic patients I see, I soon become convinced that it must be the pediatrician rather than the child who is wetting the bed. The doctor is making all the plans, deciding on the medicine, assaying the results. Over and over again in the whole field of conduct disorders, I find myself the first one to ask the child what *he* thinks to be the matter and what *he* wants to do about it. See your children *alone*. See them at other times than you see the parents. Give them, through your every action, the feeling that you have faith in their ability to solve the difficulty if they care to. And drive for the same thing with the parents—that it is for us adults to stand by the child's efforts, not to stand in place of them.

The third is hard. See the problem as the child sees it. This does not mean "solve the problem as the child has solved it." This does not mean to excuse the child; it means to understand him. It does not mean to let the child do as he will and to hell with the rest of the world; it means that you cannot change a course of action effectively unless you understand why it was undertaken. This third rule of Anna Freud's is the most difficult and most interesting of all your ventures. Often the child, in wide-eyed amazement at the first person who has tried to see what he is

trying to do, will tell you the whole problem in ten minutes. Often our myopic adult eyes and our set adult ways mean (at least in my own practice) that we never really can find out what the child is *trying to do.*

The Contribution of a Psychiatrist as a Member of the Pediatric Hospital Staff

Leo Kanner, M.D., Baltimore, Md.

Pediatricians are in agreement that a considerable number of children's problems with which they are confronted are concerned not so much with the patients' organs as with the patients themselves. They are also in agreement that their early medical training has considered largely, if not exclusively, the pathology and treatment of organs, organ systems, and more diffuse somatic diseases, but has usually neglected to include the pathology and treatment of unhealthy performances of the whole person, of the maladjusted, misbehaving, mismanaged, suffering human being. Children are brought to them daily with complaints of food capriciousness, sleep disturbances, school failures, excessive shyness or aggressiveness, anxiety, temper tantrums, breath-holding spells, restlessness, tics, nail biting, thumb-sucking, speech disorders, masturbation, and what people refer to as general nervousness. The days when all these problems were handled with the prescription pad only are fortunately over. No one realizes this more than the conscientious pediatrician himself, who is eager to learn how to deal with his patients and their parents in an informed and really helpful manner. The demand for an inclusion of psychiatric understanding in the diagnostic and therapeutic armamentarium of the pediatrician has come and grown in recent years as a spontaneous expression of this realization.

To supply this need at the Johns Hopkins Hospital, a close full-time working relationship was established in 1930 between the psychiatrist privileged to undertake this task and the staff of the Harriet Lane Home, the pediatric department of the hospital. The psychiatrist entered upon this assignment with the clear awareness of the fact that he came to learn at least as much as to teach. He considered his functions not as a chance to descend upon his pediatric collaborators with a rigid set of rules to be imposed upon them *ex cathedra,* but as a challenge to demonstrate his usefulness through practical work with the patients in whose behalf he was consulted. He did not come to create needs artifically, but to study the really existing and felt needs and help to satisfy them to the best of his ability.

For this reason, the first step was of necessity one of orientation. What were the complaints and situations that made the members of the pediatric staff feel that psychiatric assistance might contribute something to their amelioration—something which at that time was not available to themselves? The proverbial courtesy of the pediatricians led them to come to the psychiatrist with the question: What kind of cases do you want us to refer to you? However, no specifications were handed out. It was suggested that any child, regardless of the nature of his difficulty, be referred if the pediatrician felt that a consultation might be of benefit to his own understanding of the case or to the child himself. It is interesting to note what happened under the circumstances. Among the first one thousand cases selected by the pediatricians for psychiatry consultation, the leading complaints or reasons for referral were as follows (often there were two or more leading complaints in the same case):

Poor progress or conduct at school	315
Enuresis	256
Food capriciousness and pica	222
Temper tantrums	217
Nail biting	163
Restlessness	154
Fear reactions	153

Problems of epileptic children	142
Spoiled child reaction	126
Speech difficulties	124
Tics	75
Hypochondriac trends	72
Psychogenic headaches	68
Sleep disturbances	65
Sex problems	63
Psychogenic vomiting	54
Thumb-sucking	36
Crying spells	34
Stealing	29
Encopresis	26
Psychogenic constipation	24
Disobedience	22
Breath-holding spells	22
Destructiveness	21
Lying	21

A number of things were learned from this list of complaints in one thousand cases, covering a period of a little over two years. They represented a cross-section of the problems which the pediatrician meets in his daily practice. They amounted to approximately 10 per cent of all children examined and treated during that period in the Harriet Lane dispensaries, wards, special clinics, and private consultation service. The list does not include reference to the not infrequent requests for advice in the handling of delirious or stuporous children in the wards or dealing with unreasonable, belligerent, or otherwise difficult parents. Nor does it include requests for the intelligence testing of blind, deaf, orthopedically and neurologically handicapped children or those considered for adoption and for boarding home or institutional placement.

The psychiatrist regarded his functions as twofold. Aside from an unparalleled opportunity for satisfying investigative curiosities, he envisioned his task as one of helping the patients who were sent to him and at the same time imparting to the pediatricians the insight and skill necessary for the adequate handling of the common behavior disorders of children. These two functions cannot be separated. Lectures and reading assignments alone are of relatively little help. It is mainly through actual work with concrete issues that psychiatric as well as any other practical medical efficiency can be acquired. In our own setting, the amalgamation of clinical case work and clinical instruction has shaped itself in the following manner:

The referring pediatrician, when he sends a child for psychiatric consultation, is expected to formulate the problem briefly and concisely. He learns to express the facts of the complaint and his own findings and impressions lucidly in plain English, steering clear of terminologic confusions and generalizations. He thus has a chance to become aware of factors which he may have heretofore neglected, factors concerning the individual and his relations to the world in which he lives. Much is gained if the physician, in dealing with human behavior, is satisfied with the recognition and formulation of essential facts and happenings, instead of trying to translate into questionable diagnostic labels or fantastic interpretations something which he has not taken the trouble to investigate. Only those who do not appreciate the importance of clear statements of fact will be surprised to find that these simple formulations, occupying less than half a page, have been of great educational value, replacing bewildering abstractions by concrete data in everyday language.

After the child has been examined, the pediatrician receives a report which becomes an integral part of the pediatric case history and in which every step of the examination is recorded. A summary, refraining from nosologic terms, tells him: The child was brought to us with such and such a complaint. It proceeds to inform him of the patient's, his family's, teacher's, or other people's attitudes about the child and his difficulties, of the nature and development of the problem, the patient's intelligence, his emotional responses, the domestic and social implications, complicating features of his physical health, life experiences that have a bearing on the problem, and difficulties of interpersonal relationships. Recommendations are made on the basis of the findings, giving reasons for each step of the therapeutic plan and at the same time pointing out the obstacles which may lie in the way of ideal adjustment.

In addition to this, the members of the hospital staff are given an opportunity for more direct contact with the psychiatrist. The older members of the group have a standing invitation, of which they often make use, to sit in during the examination and therapeutic interviews and observe the work while it is in progress. The internes spend routinely three days a week for a period of two months at the psychiatric establishment at Harriet Lane. They see what is being done with the children and eventually learn to make themselves responsible for the taking of histories, psychiatric examinations including psychometric tests, and the working out of therapeutic programs. When they go back to the wards and dispensary, they do so with a broadened horizon, with a far better knowledge of the facts concerning children and standards of behavior. They have become less dependent on the psychiatrist in the understanding and treatment of the common personality and adjustment difficulties of their patients. They have gained a knowledge of the facilities existing in the community in behalf of maladjusted children, recreational, boarding, correctional, and custodial opportunities, and the existing possibilities of cooperation with the schools.

This arrangement is supplemented by still another mode of collaboration. The psychiatrist and his assistants are on daily call to the wards and dispensary. The pediatricians thus receive psychiatric advice not only after children had been referred, but also at the time of first contact with the patient. This takes care, among other things, of psychiatric emergencies and immediate problems in the wards, such as delirium, acute excitements, violent resentment of hospitalization, psychogenic vomiting, or excessive masturbation, at the clinic. On occasions, advice is sought and given in cases, for instance, when the parents fail to give their consent to the performance of an imperative operation or do not permit certain necessary tests to be done. In other words, the hospital physicians are aware of the presence of a psychiatrist in their midst and make use of his functions in a large variety of situations.

A similarly close relationship is maintained with the so-called special clinics of the children's hospital, the cardiac, epilepsy, endocrine, syphilis, and tuberculosis clinics. Epileptic children are referred routinely and repeatedly for assistance in home and school adjustment, intelligence rating in reasonable intervals, and vocational guidance. The pediatricians turn to us for help when a child on an antidiabetic or ketogenic diet steals prohibited food, when a rheumatic child would not stay in bed as prescribed, when a patient with severe cardiac ailment further endangers his health by fierce temper outbursts, when the sensitiveness and irritability of a choreic child become too bothersome, or when repeated psychometric tests are expected to throw light on the development of thyroid-treated cretins.

All these arrangements are governed by a spirit of mutual give-and-take collaboration. The psychiatrist has an opportunity to obtain first-hand information about many things which the average child guidance clinic, removed from a pediatric hospital, has little opportunity to learn. Being placed in the main stream of a

busy pediatric center, he sees in a constant flow the everyday problems of the everyday child as they come to the practicing pediatrician. He learns of the difficulties that may arise from hospitalization, acute illness, chronic ailments, and convalescence. He observes the problems that face the ward nurses and the social workers of the hospital. He has a chance to study the nature and extent of behavior disorders of children suffering from asthma, eczema, and spastic colon. He has a chance to follow for years the personality development of premature, rachitic, malnourished infants, of early ruminators and nystagmoid head shakers, of children with encephalitis, meningitis, epilepsy, or lead poisoning. And, above all, he has the great advantage that all his patients have had a thorough physical examination prior to being referred to him.

Just as the child psychiatrist in this manner has an opportunity to become a better child psychiatrist, so, I venture to say, does the pediatrician emerge from this arrangement as a better pediatrician. He soon learns to slough off some of the current misunderstandings about psychiatry. Some pediatricians came with the notion that psychiatry is concerned merely with extremes and end-products of mental aberrations and therefore did not see how it could possibly apply to their work with children. Some thought that it is interested merely in classifications. Some felt that it is a weird and mysterious hunt for mythologic complexes. Some thought of it in terms of hypnotism and peculiar forms of suggestion. Others believed that it was synonymous with a search for the intelligence quotient. A few had at first to overcome a definite fear of the psychiatrist whom they expected to be endowed with some supernatural powers. And some came prepared to be initiated in the use of a few quick tricks, similar to the miracles of Lourdes or the notorious chiropractic snap: You take a child, turn the magic key, and, presto, you have turned him into a perfect specimen.

The internes and other members of the staff are helped to cure themselves of these notions. They learn to humanize their patients. They learn to make themselves responsible for human beings, instead of dealing merely with collections of organs of specimens of a supposedly homogeneous species. They learn to consider the fact that some things are problems of one or another organ, others are problems of the child, still others are problems of the family and the environment, and most of them are combinations of several of these. Having learned sets of facts about tissue structures, organ functions and dysfunctions, and biochemistry, they get acquainted with new, similarly objective and concrete sets of facts about behavior, performance, the functions and dysfunctions of the individual child and his reactions to people and to life situations. They are helped to develop a curiosity for the whence and why of children's behavior disorders and are taught to satisfy this curiosity in a scientific and factual manner. They perceive that the psychiatrist who works with concrete facts can well afford and really manages to refrain from glib toying with hypothetical assumptions of unproved mechanisms and complexes. They are saved from being embarrassed by modern parents who refuse to accept at its face value the assertion that stuttering or nightmares are merely the result of bad tonsils or mild anemia. Their knowledge of pathology, limited hitherto to body structures, is broadened by the inclusion of the pathology of the acting, feeling, and reasoning person. Their knowledge of therapy is broadened by the inclusion of psychotherapy, that is, informed and understanding treatment of whole dysfunctions, of the person, the mentally integrated functioning of the individual and the group. In doing so, they are no longer likely to keep behavior problems out of their domain with an impatient shrugging of their shoulders, the prescription of tonics and sedatives, and a self-commiserating sigh which indicates: "Just another nervous, neurotic, neurasthenic, or neuropathic child!" As a matter of fact, they no longer need any of these terms if they know the child well enough and are acquainted with his problems and the proper therapeutic procedure. And they no

longer look for quick tricks but soberly and in orderly fashion use the knowledge which they have obtained in their patient work with the child, his family, his teachers, and, whenever necessary, the social agencies of the community.

Thus, the contribution of a psychiatrist as a member of a pediatric hospital staff may be summarized as follows:

1. Service to the children who are referred to him because of behavior and personality disorder.

2. Demonstration of objective, common sense methods of examination and treatment which the pediatrician can learn to use in his own practical work when dealing with common, everyday behavior difficulties of children.

3. Helping the pediatrician to assume full responsibility for the child as an individual, regardless as to whether the child does or does not present behavior difficulties.

One observation has impressed me so strongly during the six years of collaboration with the pediatric group at Harriet Lane that I cannot refrain from mentioning it briefly. Some people are in the habit of agitating themselves with the question: Who should be responsible for the handling of behavior problems of children? The psychiatrist? The pediatrician? The educator? The social worker? The psychologist? I must say that in the actual work at Harriet Lane the question of competency has not arisen even once. Its very formulation, as a matter of fact, seems to me to be based on false premises. The question should not be: Who should do this and who should do that? but: What am I prepared to do competently and what am I not prepared to do competently? I cannot see how the field of psychopathology can possibly be relegated to medically untrained people. Unless we wish to return to the medieval dualistic separation of body and mind, we must concede to the physician the right and obligation to treat sick people, whether their sickness lie in the domain of organ pathology or the pathology of the person. The psychiatrist is not competently prepared to deal with the complexities of pediatric organ pathology. Nor is the pediatrician competently prepared to deal with the complexities of psychopathology. But, without being an ophthalmologist, he has learned how to take care of uncomplicated conjunctivitis and how to use the ophthalmoscope to advantage. Without having specialized in immunology, he contributes a lion's share to the treatment and prevention of contagious diseases. And without specializing in psychiatry, he can obtain sufficient information and skill to concern himself with the everyday psychopathology and psychotherapy of childhood. This does by no means eliminate the psychiatrist, just as it does not eliminate the ophthalmologist or the immunologist. As a matter of fact, it definitely creates for him a place as an adviser and teacher of the pediatrician, who is then helped and encouraged to assume hitherto neglected responsibilities.

How do the pediatricians themselves feel about the kind of collaboration described in this presentation? The appetite for it has grown considerably in recent years. Four medical schools, those of Columbia, Western Reserve, Iowa State, and Tennessee State Universities, have made definite arrangements for a one year's training of capable and interested young pediatricians at the Harriet Lane psychiatric establishment, so that they may return to their pediatric hospitals with a knowledge of child psychiatry. The organization of this round table conference is in itself eloquent proof of this trend. Dr. Edwards A. Park, director of Johns Hopkins pediatric department, made this statement before the 1935 Conference on Psychiatric Education: "It is difficult to give an estimate of the value of the Psychiatric Clinic in the Harriet Lane Home. I feel tempted merely to say, 'We could not possibly get along without it!' On analysis, its value lies chiefly in three particulars: the care of individual children, the education of physicians and students, and the investigation of abnormal behavior in the human being. . . As a result of his instructions, Dr. Kanner has supplied the pediatric staff with the

tools for psychiatric work and has given them an ability to use those tools, for he has taught a systematic method for the examination of a child with a behavior disturbance and has made clear the principles of understanding and management."

DISCUSSION

Dr. Ebaugh asked Dr. Veeder to open the discussion.

DR. BORDEN S. VEEDER (ST. LOUIS) pointed out the great field of child psychiatry in pediatrics. He stressed the changes in the attitude of the pediatrist toward the problem during the past thirteen years. The pediatrist formerly looked upon the entire field as one of mystery shrouded in a nomenclature beyond the comprehension of the rank and file. There was a demand that the problems of child psychiatry be presented in a simpler language with a saner understanding. Dr. Veeder feels that this has been and is the job of the pediatrist as evidenced by the deeper insight displayed in attacking our everyday problems. He stressed the point that success in this field is utterly impossible without a complete understanding of the problem at hand—further, that probably no greater service can be rendered by the pediatrist in the field of child psychiatry than that of prevention. His unique position in the family, his intimate association with the child from birth, his clear understanding (as a rule) of the social, cultural and economic status of the family, his cognizance (often) of marital discord, and indeed his knowledge of most of the intimate family relationships—all these place him in a most favorable position to detect impending psychiatric problems. The alert pediatrist in his routine visits to the home, occasioned by the usual illnesses of childhood, senses the attitude of the parents and the atmosphere of the home, and he may well be in a position to predict, in his patient, the psychiatric disturbances of the future and institute even in the early months of life those measures of prevention which seem indicated. Dr. Veeder cited here in illustration the too often encountered psychogenic constipation, having for its background the overanxious mother obsessed with the necessity that her baby have a daily evacuation of the bowels at a stated time. The child finally "feels" the worry of the mother and becomes equally concerned with the problem. Such disturbances can and should be anticipated by the pediatrist and prevented. His close observation of the attitude and atmosphere of the baby's environment will enable him to be successful in meeting these situations. To do this he must develop an analytical attitude.

Dr. Veeder contrasted the position of the pediatrist in the home of the patient with that of the psychiatrist who meets the patient only in his office; he stated that he felt the former had certain distinct advantages. He further stated that, although he appreciated the value of the social worker in child psychiatry, her importance had been definitely overemphasized. His own contacts with the family in the home provided ample opportunity for study of environment and relations from which study he finds no trouble in estimating his ability to handle the problem.

DR. C. ANDERSON ALDRICH (WINNETKA, ILL.) stressed the importance of attitude in the field of child psychiatry. He emphasized the point that attitude, not knowledge, was the all-important feature in dealing with these problems, and finally raised the question "Is attitude contagious?"

CHAIRMAN EBAUGH stated that attitude must be considered in all problems, especially in school where he believes attitude is undoubtedly transmitted from teacher to child. As an example, he cited the instance of thyrotoxicosis in the teacher, with its resulting effect upon the students.

DR. HENRY F. HELMHOLZ (ROCHESTER, MINN.) feels that the pediatrist is probably responsible for the "worry attitude" so frequently encountered in the mother. The importance placed upon the child's routine as to habits of food,

stool, rest, etc., has been carried to extreme. He believes that the pediatrist appreciates this situation and is getting away from its overemphasis. Dr. Helmholz drew attention to the absolute necessity, in dealing with psychiatric disturbances, of getting at the *child's* problem as in contrast to the mother's problem.

CHAIRMAN EBAUGH asked how and under what circumstances do pediatrists refer their cases to psychiatrists. He discouraged the "last resort" attitude which so frequently is assumed by both pediatrist and parent toward the psychiatrist. He rather took the pediatrist to task for the superficial manner in which the referred case is studied before reaching the psychiatrist.

DR. VEEDER took exception to a statement made by Dr. Ebaugh in his leading discussion that the pediatrist should do his own Binet-Simon tests. He feels that the trained psychiatric worker should actually carry out the technic of the test, after which the pediatrist should interpret the findings.

CHAIRMAN EBAUGH stated that, not only is the technic of the test of value, but the attitude of the child toward the test is of great importance and therefore well worth the time consumed in its doing.

DR. GUSTAVE F. WEINFELD (RAVINIA, ILL.) stated that he feels it is extremely difficult for the pediatrist to get at the root of these psychiatric disturbances. The time-consuming investigations necessary to arrive at a proper understanding of the hereditary and environmental phases of the problem and the proper evaluation of the social and family relations are well-nigh impossible for the pediatrist.

CHAIRMAN EBAUGH feels that the situation is not so hopeless as depicted. Often the problem is found in the parent's attitude. Oversolicitude probably is encountered most often, resulting in the overprotected child, the dependent child devoid of initiative. At times the solution is found in some very obvious occurrence in the family life, such as illness or death; at other times, in the more obscure family relationships, such as marital difficulties, etc. Finally, Dr. Ebaugh suggested that the pediatrist might enlist the service of a trained psychiatric worker.

DR. KANNER stressed the importance of working with the child himself. Get the problem from the child; the parent sees it intellectually, not emotionally.

DR. CARROLL M. POUNDERS (OKLAHOMA CITY, OKLA.) asked Dr. Kanner whether he believes that allergic children have inherent nervous make-up.

DR. KANNER stated that the allergic child is not essentially neurotic. Much depends on attitude of parent toward allergic condition. He feels that all such terms as neuropathic, neurotic, congenital neuropath, be discarded and that only the particular problem in the particular child be considered.

DR. VEEDER emphasized the importance of inherent characteristics as opposed to environment in any consideration of growth and development. He asked if it is not logical to assume the existence of a congenital emotional type.

DR. PLANT disliked the term "congenital emotional type." He prefers to speak of the vulnerability of the individual. It is important to determine the load which a child can stand. It is found remarkably consistent and can be fairly accurately predicted throughout childhood.

He feels that attitudes are most certainly contagious. Attitudes are communicated through psychomotor tensions. It is the *way* things are said, not *what* is said. It is impossible to explain attitudes—one shows faith in them. Finally, Dr. Plant took issue with Dr. Veeder in regard to the pediatrist's knowledge of family relations. He feels that the pediatrist is unable to learn much of the environment and interrelationships as he encounters the family in the home. The parents are dressed up mentally and physically for the physician's visit; only the trained psychiatric social worker and nurse see the family undressed.

DR. ALDRICH.—In what does inability to bear load consist? Might the violent reaction of certain newborn infants to their environment mean that in later infancy and childhood such children would be unable to bear the expected load?

DR. PLANT.—Yes.

DR. STANLEY D. GIFFEN (TOLEDO, OHIO).—What are the commoner problems the child is attempting to meet when enuresis is established?

DR. PLANT.—1. Desire to regain the preeminence of babyhood, as when the new baby arrives.

2. Responding to the family's interest in enuresis. The parent is interested in the wrong thing instead of the right. The child appreciates this—only by concentration on wrong things does he get attention.

3. Playing with older child—carrying the load of an eight-year-old by a six-year-old may produce enuresis. Sometimes in school the child is carrying a load too heavy for his mental and physical make-up.

Finally, Dr. Plant advised: Do not concentrate on enuresis; concentrate on the child's problem.

DR. LEROY A. WILKES (TRENTON, N. J.).—Who knows the family? Granted the pediatrist in his contact is unable to learn the true situation while the visiting nurse does get at the root of the problem, does her success depend upon technic or is it simply a matter of her continued presence breaking down resistance?

DR. PLANT.—Her success does not depend upon any technic which is not available to the pediatrist. She is more one of the family. The mother gets off her dignity. The time element probably plays a less important rôle than the intimacy of the relationship.

CHAIRMAN EBAUGH criticized the pediatrist for the manner in which cases are referred to the psychiatrist. Typical of the pediatrist's so-called diagnosis on these cases might be mentioned such terms as "neurotic child," "hyperactive child," "terrible delinquency," etc. Most of the children present very definite problems. The diagnoses or labels as applied by pediatrists mean nothing. He asked the question: What is the pediatric technic in average personality and emotional problems?

DR. VEEDER.—The technic employed by the pediatrist is much the same as that of the psychiatrist when and if the case is investigated at all. Dr. Veeder reiterated that he feels the pediatrist *does* know the family by his visits to the home. He anticipates impending problems and institutes measures of prevention in the early years.

DR. PLANT warned against the possibility of producing fear of what may come by adopting Dr. Veeder's idea of prevention.

DR. KANNER, discussing further technic, emphasized the importance of an intelligent story of the family, its environment and problems, rather than the stereotyped history so frequently obtained. He was particularly bitter against the "Father L & W, Mother L & W" type of history. He urged that the mother be given full range to tell her own story as she chooses. She should be taken seriously.

DR. JOHN A. BIGLER (HIGHLAND PARK, ILL.).—How does one get information from the child? How does one find out why the child is doing what he is doing?

DR. KANNER.—Obtain information first from parent, school, physician, social worker, nurse, and then from child. The interview with the child should not be a third degree. The questions should be simple, the answers taken seriously; get his reason for his behavior.

DR. PLANT stated that his technic is different from Dr. Kanner's. He interviews the child first and knows absolutely nothing about him at the first conference. He allows the child to tell his own story, beginning with his first memories. The child should not be asked why he commits his digression; this immediately places him on the defensive; rather he should be guided in telling his own story of himself, and in the nature of things he finally works into the problem itself. Above all else, keep faith with the child. Do not be jockeyed into the position of a whip for the family.

DR. H. K. TENNEY, JR. (MADISON, WIS.).—What can we do toward the prevention of difficulties? How can we educate the parents to anticipate the problems?

DR. KANNER.—Prevention is difficult, but by solving one problem the parent gains confidence and comes with the new ones before they are too advanced. Give the parent confidence in dealing with problems. Do not frighten him by anticipating the problems too much. Have the parents steer clear of confusion.

DR. PLANT: Dr. Tenney's question has always been of great interest to me. Teachers can do things with other children that they cannot do with their own. The love factor complicates matters. It removes objectivity and blinds parents so they cannot see the important facts.

DR. LANDY.—Are not the factors in the problem so many as to defy solution?

DR. KANNER.—Parents come to us with a definite problem. We must examine the physical and environmental factors and try to help as much as possible. Often the outstanding difficulty cannot be removed, but we do the best we can to help the situation.

DR. P. J. ZENTAY (ST. LOUIS).—How can we discover the problem of parent-child relationship early? Most of the problems can be traced to the first few months of life. Overanxiety of the mother over the possible difficulties that may arise should be handled by the pediatrician. We are dealing with a complexity of personalities, and, if we cannot influence the parents, nothing can be done. Our entire work is premised on the fact that we can influence the parents.

DR. KANNER.—I thought I was in for a fight, but I see you agree with me. I feel that genus homo will improve. I see children at four to five months. It is a challenge to pediatricians to start work with the parents when the children are at that age, to keep them from getting false anxieties, which do so much harm. Psychiatry in the last thirty years has rediscovered common sense.

CHAIRMAN EBAUGH.—An analysis of 500 cases has shown that oversolicitude, and overprotection have been the chief causes of temper tantrums, daydreaming, and hypochondriasis. In adolescence those children remain overdependent on their parents and are emotionally retarded. Parents should be made aware of this condition so they can correct it.

DR. MITCHELL.—Parents have an idea that all their children can reach the higher grades. Are not graded schools bad?

DR. PLANT.—We must go into the schools and teach them what to do. In our county we have done away with the Binet classes. We must carry the child along according to his chronologic age. Special classes are garbage heaps and should be done away with. We are realizing that school is life, not just a preparation for life. The child should live to the fullest each year of his life. This idea is gaining hold. The fullness of a child's adult life depends on the fullness of his child life. With regard to attitudes, they cannot be taught by words, but only by example.

DR. BUFFORD.—Do you think that the school report cards cause conflicts in a child?

DR. PLANT.—Yes. We are trying out a card without grades. It is general, showing the strengths and weaknesses of the child without resorting to figures. The usual grade report cards do much damage.

DR. MITCHELL.—How long are you going to keep the children in school?

DR. PLANT.—An enormous number of children who would otherwise be working are forced to remain in school, due to the economic depression. The schools are facing unusual and unprecedented problems, but I believe it is a good thing for them. They will solve them by getting away from their academic tradition and so will prepare the child for life.

CHAIRMAN EBAUGH.—I am concerned with two things now:

1. Why the doctors are not using psychiatric social service workers to deal with behavior problems in private practice.

2. The lack of information accompanying the case when the child is referred to a psychiatrist. Labels like nervousness, incorrigibility, etc., are meaningless. Formulate the complaints in chronologic order. Give the complete history as it is told to you and all the pertinent facts.

DR. TENNEY.—This sort of conference lets us see what we are expected to do. To most of us the expense of a psychiatric social worker is prohibitive.

DR. ZENTAY.—The pediatrician cannot use this method because of the small fee he commands. The problem child requires long consultations with the parents for which they are willing to pay only the general charge for an office call.

DR. KANNER.—The time factor is very important. I am aware of it. But how little time it takes to do harm. Parents can easily be frightened by having them anticipate illnesses and by exaggerating symptoms. By learning the technic, the time required in handling these cases can be shortened. Listen to the complaint. Find out the situation. By educating the parents, they will be willing to pay for the extra time.

M. HINES ROBERTS, Recorder.

News and Notes

The following physicians have been certified by the **American Board of Pediatrics** since the last report. Twenty-three of these men were examined.

John A. Bigler, Highland Park, Ill.
Arthur Proctor Black, Peiping, China
Frederick B. Burke, Detroit, Mich.
Garabed A. Z. Garabedian, Tulsa, Okla.
Flora K. Rubinstein, Brooklyn, N. Y.
Harry Apfel, Brooklyn, N. Y.
Samuel Sheppard Brown, Brooklyn, N. Y.
John B. Burns, Binghamton, N. Y.
John Walker Canaday, Glens Falls, N. Y.
Fred T. Cavanaugh, Troy, N. Y.
John Frank Coppolino, Philadelphia, Pa.
Louis Klein Diamond, Boston, Mass.
Katherine Jean Edgar, Rochester, N. Y.
H. Louis George, Jr., Watertown, N. Y.
George Courtenay Glass, Jr., Hartford, Conn.
Edward Scott Goodwin, Albany, N. Y.
Milton J. H. Grand, New York, N. Y.
John Bolter Griggs, Hartford, Conn.
Irving LeBell, New York, N. Y.
Walter Levy, New York, N. Y.
Charles H. O'Regan, New York, N. Y.
William Panitch, Newark, N. J.
Henry Nickerson Pratt, Boston, Mass.
Hugh Currie Thompson, Jr., Albany, N. Y.
Henry Woodruff Titus, New Rochelle, N. Y.
J. Alfred Trackman, New York, N. Y.
Mark J. Wallfield, Brooklyn, N. Y.
Henry Washeim, Jr., Utica, N. Y.

Comments

Nearly fifteen years ago the Section on Pediatrics of the American Medical Association voted to establish the Abraham Jacobi Memorial Fund. Each subscriber to the fund receives a copy of the current *Transactions of the Section on Pediatrics*, and the balance of the money is used by the fund to pay the expenses of guest speakers, special publications, special committee expenses, and the like. As a balance gradually accumulated, it was voted several years later to accumulate an endowment fund of $10,000. Approximately $6,000 was accumulated and invested in this way, to which $2,000 was added by a gift from the Central States Pediatric Society. When the latter was disbanded to form Section III and part of Section II of the American Academy of Pediatrics, it was voted to turn over the funds remaining in the treasury to the Jacobi Memorial Fund. The endowment fund thus stands at approximately $8,000 at the present time. When the endowment fund was founded, it was with the idea that an endowment of $10,000 would produce an annual income of $500, and no further annual subscriptions would be necessary.

In the early days of the fund the usual subscription was $5 although many contributed more to get the endowment fund under way. There has been a steady decline in the number of subscribers in the past four years. The Fund Committee, consisting of the last four Section chairmen, with the secretary, Dr. Frank Neff, of Kansas City, whose individual work and interest over these years has to a large extent been responsible for the success of the fund, has recently circularized the friends of the Section in regard to the fund and transactions. The American Medical Association must be guaranteed a minimum distribution of 350 copies if the Transactions are to be continued. The Fund Committee is reducing the amount asked from each subscriber to $3. It is hoped by this means to increase the number of subscribers to the fund. The fund has served a useful purpose and has aided materially in the work of the Section and in furthering worthwhile pediatric projects. It has been carefully managed, and the committee deserves our support as well as our thanks. The question is raised as to whether the *Transactions of the Section on Pediatrics* should be continued. While from a sentimental standpoint the older members would dislike to see the Transactions discontinued, the value of publishing together a group of articles on unrelated subjects, all of which are published elsewhere, is questionable.

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